=> fil reg
FILE 'REGISTRY' ENTERED AT 15:43:41 ON 13 JUL 2004

Property values tagged with IC are from the ZIC/VINITI data file provided by InfoChem.

STRUCTURE FILE UPDATES: 11 JUL 2004 HIGHEST RN 708207-86-7
DICTIONARY FILE UPDATES: 11 JUL 2004 HIGHEST RN 708207-86-7

TSCA INFORMATION NOW CURRENT THROUGH JANUARY 6, 2004

Please note that search-term pricing does apply when conducting SmartSELECT searches.

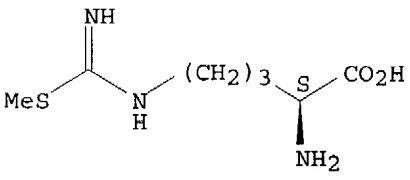
Crossover limits have been increased. See HELP CROSSOVER for details.

Experimental and calculated property data are now available. For more information enter HELP PROP at an arrow prompt in the file or refer to the file summary sheet on the web at:
http://www.cas.org/ONLINE/DBSS/registryss.html

=> d ide l86 1-17; d ide l87 1-9

L86 ANSWER 1 OF 17 REGISTRY COPYRIGHT 2004 ACS on STN
RN **156719-41-4** REGISTRY
CN L-Ornithine, N5-[imino(methylthio)methyl]- (9CI) (CA INDEX NAME)
OTHER NAMES:
CN S-Methyl-L-thiocitrulline
CN S-Methylthiocitrulline
CN S-MTC
FS STEREOSEARCH
MF C7 H15 N3 O2 S
CI COM
SR CA
LC STN Files: BIOSIS, CA, CANCERLIT, CAPLUS, CEN, CHEMCATS, CSCHEM, MEDLINE, PROUSDDR, TOXCENTER, USPAT2, USPATFULL
DT.CA CAplus document type: Journal; Patent
RL.P Roles from patents: BIOL (Biological study); PREP (Preparation); PROC (Process); USES (Uses)
RLD.P Roles for non-specific derivatives from patents: BIOL (Biological study); USES (Uses)
RL.NP Roles from non-patents: ANST (Analytical study); BIOL (Biological study); PREP (Preparation); PROC (Process); PRP (Properties); USES (Uses)

Absolute stereochemistry. Rotation (+).



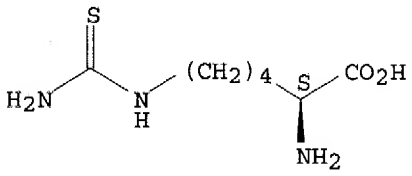
PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

42 REFERENCES IN FILE CA (1907 TO DATE)

1 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
42 REFERENCES IN FILE CAPLUS (1907 TO DATE)

L86 ANSWER 2 OF 17 REGISTRY COPYRIGHT 2004 ACS on STN
RN **156719-38-9** REGISTRY
CN L-Lysine, N6-(aminothioxomethyl)- (9CI) (CA INDEX NAME)
OTHER NAMES:
CN **L-Homothiocitrulline**
FS STEREOSEARCH
MF C7 H15 N3 O2 S
CI COM
SR CA
LC STN Files: CA, CAPLUS, TOXCENTER, USPATFULL
DT.CA CAplus document type: Journal; Patent
RL.P Roles from patents: BIOL (Biological study); PREP (Preparation); USES (Uses)
RL.NP Roles from non-patents: PREP (Preparation)

Absolute stereochemistry.

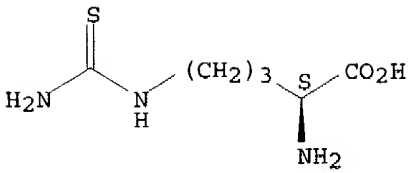


PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

5 REFERENCES IN FILE CA (1907 TO DATE)
5 REFERENCES IN FILE CAPLUS (1907 TO DATE)

L86 ANSWER 3 OF 17 REGISTRY COPYRIGHT 2004 ACS on STN
RN **156719-37-8** REGISTRY
CN L-Ornithine, N5-(aminothioxomethyl)- (9CI) (CA INDEX NAME)
OTHER NAMES:
CN L-TC
CN **L-Thiocitrulline**
FS STEREOSEARCH
MF C6 H13 N3 O2 S
CI COM
SR CA
LC STN Files: BIOSIS, CA, CAPLUS, CHEMCATS, CSCHEM, TOXCENTER, USPATFULL
DT.CA CAplus document type: Journal; Patent
RL.P Roles from patents: BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)
RLD.P Roles for non-specific derivatives from patents: BIOL (Biological study); USES (Uses)
RL.NP Roles from non-patents: ANST (Analytical study); BIOL (Biological study); PREP (Preparation); PROC (Process); PRP (Properties); USES (Uses)
RLD.NP Roles for non-specific derivatives from non-patents: BIOL (Biological study); PREP (Preparation)

Absolute stereochemistry.

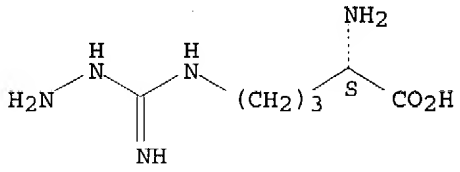


PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

43 REFERENCES IN FILE CA (1907 TO DATE)
3 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
43 REFERENCES IN FILE CAPLUS (1907 TO DATE)

L86 ANSWER 4 OF 17 REGISTRY COPYRIGHT 2004 ACS on STN
RN **57444-72-1** REGISTRY
CN L-Ornithine, N5-(hydrazinoiminomethyl)- (9CI) (CA INDEX NAME)
OTHER NAMES:
CN NG-Amino-L-arginine
FS STEREOSEARCH
MF C6 H15 N5 O2
CI COM
LC STN Files: CA, CANCERLIT, CAPLUS, MEDLINE, TOXCENTER, USPAT2, USPATFULL
DT.CA CAplus document type: Journal; Patent
RL.P Roles from patents: BIOL (Biological study); PREP (Preparation); USES (Uses)
RLD.P Roles for non-specific derivatives from patents: PREP (Preparation)
RL.NP Roles from non-patents: BIOL (Biological study); PREP (Preparation); PROC (Process); PRP (Properties)

Absolute stereochemistry.



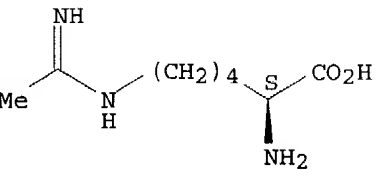
PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

48 REFERENCES IN FILE CA (1907 TO DATE)
1 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
48 REFERENCES IN FILE CAPLUS (1907 TO DATE)

L86 ANSWER 5 OF 17 REGISTRY COPYRIGHT 2004 ACS on STN
RN **53774-63-3** REGISTRY
CN L-Lysine, N6-(1-iminoethyl)- (9CI) (CA INDEX NAME)
OTHER NAMES:
CN .epsilon.-Acetimidyllysine
CN L-NIL
FS STEREOSEARCH
MF C8 H17 N3 O2
CI COM
LC STN Files: ANABSTR, BIOSIS, BIOTECHNO, CA, CAPLUS, CHEMCATS, EMBASE, PROUSDDR, TOXCENTER, USPATFULL
DT.CA CAplus document type: Journal; Patent
RL.P Roles from patents: BIOL (Biological study); PREP (Preparation); USES

(Uses)
RLD.P Roles for non-specific derivatives from patents: BIOL (Biological study); PREP (Preparation); USES (Uses)
RL.NP Roles from non-patents: ANST (Analytical study); BIOL (Biological study); PREP (Preparation); PROC (Process); PRP (Properties); USES (Uses)
RLD.NP Roles for non-specific derivatives from non-patents: BIOL (Biological study)

Absolute stereochemistry.

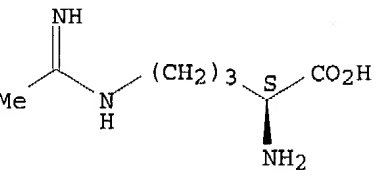


PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

85 REFERENCES IN FILE CA (1907 TO DATE)
2 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
85 REFERENCES IN FILE CAPLUS (1907 TO DATE)

L86 ANSWER 6 OF 17 REGISTRY COPYRIGHT 2004 ACS on STN
RN **36889-13-1** REGISTRY
CN L-Ornithine, N5-(1-iminoethyl)- (9CI) (CA INDEX NAME)
OTHER NAMES:
CN L-NIO
CN N.delta.-(Iminoethyl)-L-ornithine
CN N5-(1-Iminoethyl)-L-ornithine
FS STEREOSEARCH
MF C7 H15 N3 O2
CI COM
LC STN Files: BIOSIS, BIOTECHNO, CA, CANCERLIT, CAPLUS, CHEMCATS, CSCHEM, EMBASE, MEDLINE, TOXCENTER, USPAT2, USPATFULL
DT.CA CAplus document type: Dissertation; Journal; Patent
RL.P Roles from patents: ANST (Analytical study); BIOL (Biological study); PREP (Preparation); PROC (Process); USES (Uses)
RLD.P Roles for non-specific derivatives from patents: BIOL (Biological study); USES (Uses)
RL.NP Roles from non-patents: ANST (Analytical study); BIOL (Biological study); FORM (Formation, nonpreparative); PREP (Preparation); PROC (Process); PRP (Properties); USES (Uses)
RLD.NP Roles for non-specific derivatives from non-patents: BIOL (Biological study); PREP (Preparation)

Absolute stereochemistry.

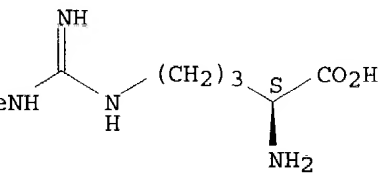


PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

112 REFERENCES IN FILE CA (1907 TO DATE)
2 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
112 REFERENCES IN FILE CAPLUS (1907 TO DATE)

6 ANSWER 7 OF 17 REGISTRY COPYRIGHT 2004 ACS on STN
17035-90-4 REGISTRY
L-Ornithine, N5-[imino(methylamino)methyl]- (9CI) (CA INDEX NAME)
THER CA INDEX NAMES:
Ornithine, N5-(methylamidino)-, L- (8CI)
THER NAMES:
.omega.-N-Methylarginine
.omega.-N-Monomethylarginine
L-Monomethylarginine
L-NG-Methylarginine
L-NMA
L-NMMA
Methylarginine
N5-(Methylamidino)-L-ornithine
NG-Methyl-L-arginine
NG-methyl-L-arginine
NG-Methylarginine
NG-Monomethyl-L-arginine
NG-Monomethylarginine
Targinine
STEREOSEARCH
42342-68-7
C7 H16 N4 O2
COM
STN Files: ADISINSIGHT, ADISNEWS, AGRICOLA, ANABSTR, BEILSTEIN*, BIOSIS, BIOTECHNO, CA, CANCERLIT, CAPLUS, CASREACT, CHEMCATS, CHEMINFORMRX, CIN, CSCHEM, DDFU, DRUGU, EMBASE, IMSPATENTS, IMSRESEARCH, IPA, MEDLINE, PHAR, PROMT, PROUSDDR, RTECS*, SYNTHLINE, TOXCENTER, USAN, USPAT2, USPATFULL
(*File contains numerically searchable property data)
.CA CAplus document type: Conference; Journal; Patent
.P Roles from patents: ANST (Analytical study); BIOL (Biological study); PREP (Preparation); PROC (Process); RACT (Reactant or reagent); USES (Uses)
LD.P Roles for non-specific derivatives from patents: BIOL (Biological study); USES (Uses)
.NP Roles from non-patents: ANST (Analytical study); BIOL (Biological study); FORM (Formation, nonpreparative); OCCU (Occurrence); PREP (Preparation); PROC (Process); PRP (Properties); RACT (Reactant or reagent); USES (Uses)
LD.NP Roles for non-specific derivatives from non-patents: BIOL (Biological study); OCCU (Occurrence)

bsolute stereochemistry.

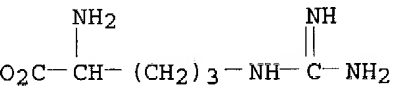


*PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT**

879 REFERENCES IN FILE CA (1907 TO DATE)
3 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA

879 REFERENCES IN FILE CAPLUS (1907 TO DATE)

86 ANSWER 8 OF 17 REGISTRY COPYRIGHT 2004 ACS on STN
N 7200-25-1 REGISTRY
N **Arginine (9CI)** (CA INDEX NAME)
THER CA INDEX NAMES:
N Arginine, DL- (8CI)
N DL-Arginine
THER NAMES:
N (.+-.)-Arginine
S 3D CONCORD
F C6 H14 N4 O2
I COM
C STN Files: ADISNEWS, AGRICOLA, ANABSTR, BEILSTEIN*, BIOBUSINESS, BIOSIS, CA, CAPLUS, CASREACT, CEN, CHEMCATS, CHEMLIST, CIN, CSCHEM, DETHERM*, DIOGENES, GMELIN*, HODOC*, HSDB*, IFICDB, IFIPAT, IFIUDB, MEDLINE, NAPRALERT, PIRA, PROMT, TOXCENTER, TULSA, USPAT2, USPATFULL
(*File contains numerically searchable property data)
Other Sources: EINECS**, NDSL**, TSCA**
(**Enter CHEMLIST File for up-to-date regulatory information)
T.CA CAplus document type: Conference; Journal; Patent
L.P Roles from patents: ANST (Analytical study); BIOL (Biological study); FORM (Formation, nonpreparative); PREP (Preparation); PROC (Process); RACT (Reactant or reagent); USES (Uses); NORL (No role in record)
LD.P Roles for non-specific derivatives from patents: BIOL (Biological study); USES (Uses)
L.NP Roles from non-patents: ANST (Analytical study); BIOL (Biological study); FORM (Formation, nonpreparative); MSC (Miscellaneous); OCCU (Occurrence); PREP (Preparation); PROC (Process); PRP (Properties); RACT (Reactant or reagent); USES (Uses); NORL (No role in record)
LD.NP Roles for non-specific derivatives from non-patents: ANST (Analytical study); BIOL (Biological study); PREP (Preparation); PROC (Process); PRP (Properties); RACT (Reactant or reagent)



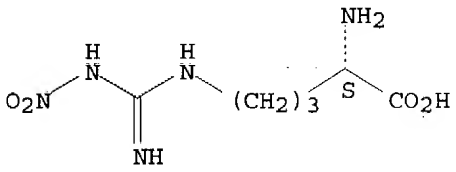
*PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT**

319 REFERENCES IN FILE CA (1907 TO DATE)
16 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
319 REFERENCES IN FILE CAPLUS (1907 TO DATE)

86 ANSWER 9 OF 17 REGISTRY COPYRIGHT 2004 ACS on STN
N **2149-70-4** REGISTRY
N L-Ornithine, N5-[imino(nitroamino)methyl]- (9CI) (CA INDEX NAME)
THER CA INDEX NAMES:
N Ornithine, N5-(nitroamidino)-, L- (8CI)
THER NAMES:
N (+)-NG-Nitroarginine
N .omega.-Nitro-L-arginine
N .omega.-Nitroarginine
N L-Arginine, .omega.-nitro-
N L-Arginine, NG-nitro-
N L-NG-Nitroarginine
N L-NNA
N N.omega.-Nitro-L-arginine
N N.omega.-Nitro-L-arginine

CN NG-Nitro-L-arginine
CN NG-Nitroarginine
CN Nitro-L-arginine
CN Nitroarginine
CN NOLA
CN NSC 53662
FS STEREOSEARCH
DR 13855-78-2, 126265-23-4, 38733-00-5
MF C6 H13 N5 O4
CI COM
LC STN Files: ADISNEWS, AGRICOLA, BEILSTEIN*, BIOBUSINESS, BIOSIS, BIOTECHNO, CA, CANCERLIT, CAOLD, CAPLUS, CASREACT, CHEMCATS, CHEMLIST, CIN, CSCHEM, DDFU, DRUGU, EMBASE, IFICDB, IFIPAT, IFIUDB, IPA, MEDLINE, PROMT, PROUSDDR, RTECS*, SPECINFO, TOXCENTER, USPAT2, USPATFULL
(*File contains numerically searchable property data)
Other Sources: EINECS**, NDSL**, TSCA**
(**Enter CHEMLIST File for up-to-date regulatory information)
DT.CA CAplus document type: Conference; Dissertation; Journal; Patent
RL.P Roles from patents: BIOL (Biological study); PREP (Preparation); PROC (Process); RACT (Reactant or reagent); USES (Uses)
RLD.P Roles for non-specific derivatives from patents: ANST (Analytical study); BIOL (Biological study); PREP (Preparation); PROC (Process); RACT (Reactant or reagent); USES (Uses)
RL.NP Roles from non-patents: ANST (Analytical study); BIOL (Biological study); FORM (Formation, nonpreparative); OCCU (Occurrence); PREP (Preparation); PROC (Process); PRP (Properties); RACT (Reactant or reagent); USES (Uses); NORL (No role in record)
RLD.NP Roles for non-specific derivatives from non-patents: BIOL (Biological study); PREP (Preparation); PRP (Properties); RACT (Reactant or reagent)

Absolute stereochemistry.

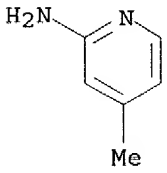


PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

962 REFERENCES IN FILE CA (1907 TO DATE)
21 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
963 REFERENCES IN FILE CAPLUS (1907 TO DATE)
2 REFERENCES IN FILE CAOLD (PRIOR TO 1967)

L86 ANSWER 10 OF 17 REGISTRY COPYRIGHT 2004 ACS on STN
RN **695-34-1** REGISTRY
CN 2-Pyridinamine, 4-methyl- (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN 4-Picoline, 2-amino- (7CI, 8CI)
OTHER NAMES:
CN (4-Methylpyridin-2-yl)amine
CN 2-Amino-.gamma.-picoline
CN 2-Amino-4-methylpyridine
CN 2-Amino-4-picoline
CN 4-Methyl-2-aminopyridine
CN 4-Methyl-2-pyridinamine
CN 4-Methyl-2-pyridylamine
CN Aminopicoline

CN Ascensil
CN NSC 1490
CN NSC 176165
CN NSC 6972
CN RA 1226
CN VMI 20-4
CN W 45
CN W 45 Raschig
FS 3D CONCORD
DR 135995-51-6
MF C6 H8 N2
CI COM
LC STN Files: ANABSTR, BEILSTEIN*, BIOSIS, BIOTECHNO, CA, CAOLD, CAPLUS, CASREACT, CHEMCATS, CHEMINFORMRX, CHEMLIST, CIN, CSCHEM, DDFU, DRUGU, EMBASE, GMELIN*, HODOC*, IFICDB, IFIPAT, IFIUDB, MEDLINE, MRCK*, PS, RTECS*, SPECINFO, SYNTHLINE, TOXCENTER, USPAT2, USPATFULL
(*File contains numerically searchable property data)
Other Sources: EINECS**, NDSL**, TSCA**
(**Enter CHEMLIST File for up-to-date regulatory information)
DT.CA CAplus document type: Conference; Journal; Patent; Report
RL.P Roles from patents: ANST (Analytical study); BIOL (Biological study); PREP (Preparation); PROC (Process); PRP (Properties); RACT (Reactant or reagent); USES (Uses); NORL (No role in record)
RLD.P Roles for non-specific derivatives from patents: BIOL (Biological study); PREP (Preparation); PRP (Properties); RACT (Reactant or reagent); USES (Uses)
RL.NP Roles from non-patents: ANST (Analytical study); BIOL (Biological study); FORM (Formation, nonpreparative); OCCU (Occurrence); PREP (Preparation); PROC (Process); PRP (Properties); RACT (Reactant or reagent); USES (Uses); NORL (No role in record)
RLD.NP Roles for non-specific derivatives from non-patents: BIOL (Biological study); FORM (Formation, nonpreparative); PREP (Preparation); PRP (Properties); RACT (Reactant or reagent); USES (Uses)

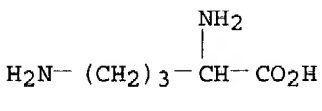


PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

815 REFERENCES IN FILE CA (1907 TO DATE)
15 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
817 REFERENCES IN FILE CAPLUS (1907 TO DATE)
16 REFERENCES IN FILE CAOLD (PRIOR TO 1967)

L86 ANSWER 11 OF 17 REGISTRY COPYRIGHT 2004 ACS on STN
RN 616-07-9 REGISTRY
CN **Ornithine (9CI)** (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN DL-Ornithine
CN Ornithine, DL- (8CI)
OTHER NAMES:
CN (.+-.)-Ornithine
CN (RS)-Ornithine
FS 3D CONCORD
MF C5 H12 N2 O2

CI COM
LC STN Files: ADISNEWS, AGRICOLA, ANABSTR, BEILSTEIN*, BIOBUSINESS, BIOSIS, CA, CAPLUS, CASREACT, CHEMLIST, CIN, CSCHEM, DETHERM*, GMELIN*, IFICDB, IFIPAT, IFIUDB, MEDLINE, MRCK*, NAPRALERT, PROMT, TOXCENTER, TULSA, USPATFULL
(*File contains numerically searchable property data)
Other Sources: EINECS**
(**Enter CHEMLIST File for up-to-date regulatory information)
DT.CA CAplus document type: Conference; Dissertation; Journal; Patent
RL.P Roles from patents: ANST (Analytical study); BIOL (Biological study); PREP (Preparation); PROC (Process); PRP (Properties); RACT (Reactant or reagent); USES (Uses); NORL (No role in record)
RLD.P Roles for non-specific derivatives from patents: BIOL (Biological study); USES (Uses)
RL.NP Roles from non-patents: ANST (Analytical study); BIOL (Biological study); FORM (Formation, nonpreparative); OCCU (Occurrence); PREP (Preparation); PROC (Process); PRP (Properties); RACT (Reactant or reagent); USES (Uses); NORL (No role in record)
RLD.NP Roles for non-specific derivatives from non-patents: BIOL (Biological study); FORM (Formation, nonpreparative); PREP (Preparation); PROC (Process); PRP (Properties); RACT (Reactant or reagent)



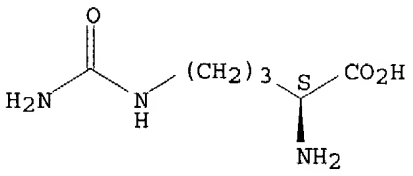
PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

262 REFERENCES IN FILE CA (1907 TO DATE)
23 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
262 REFERENCES IN FILE CAPLUS (1907 TO DATE)

L86 ANSWER 12 OF 17 REGISTRY COPYRIGHT 2004 ACS on STN
RN 372-75-8 REGISTRY
CN L-Ornithine, N5-(aminocarbonyl)- (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN Ornithine, N5-carbamoyl-, L- (8CI)
OTHER NAMES:
CN .alpha.-Amino-.delta.-ureidovaleric acid
CN .delta.-Ureidonorvaline
CN **Citrulline**
CN L-Citrulline
CN N.delta.-Carbamylornithine
CN N5-Carbamoyl-L-ornithine
CN NSC 27425
FS STEREOSEARCH
MF C6 H13 N3 O3
CI COM
LC STN Files: ADISNEWS, AGRICOLA, ANABSTR, BEILSTEIN*, BIOBUSINESS, BIOSIS, BIOTECHNO, CA, CANCERLIT, CAOLD, CAPLUS, CASREACT, CEN, CHEMCATS, CHEMINFORMRX, CHEMLIST, CIN, CSCHEM, DDFU, DRUGU, EMBASE, HODOC*, IFICDB, IFIPAT, IFIUDB, IPA, MEDLINE, MRCK*, MSDS-OHS, NAPRALERT, NIOSHTIC, PIRA, PROMT, PS, SPECINFO, TOXCENTER, USPAT2, USPATFULL, VETU
(*File contains numerically searchable property data)
Other Sources: EINECS**, NDSL**, TSCA**
(**Enter CHEMLIST File for up-to-date regulatory information)
DT.CA CAplus document type: Conference; Dissertation; Journal; Patent; Report
RL.P Roles from patents: ANST (Analytical study); BIOL (Biological study); FORM (Formation, nonpreparative); OCCU (Occurrence); PREP (Preparation);

PROC (Process); PRP (Properties); RACT (Reactant or reagent); USES (Uses); NORL (No role in record)
RLD.P Roles for non-specific derivatives from patents: ANST (Analytical study); BIOL (Biological study); PREP (Preparation); PROC (Process); PRP (Properties); USES (Uses)
RL.NP Roles from non-patents: ANST (Analytical study); BIOL (Biological study); FORM (Formation, nonpreparative); MSC (Miscellaneous); OCCU (Occurrence); PREP (Preparation); PROC (Process); PRP (Properties); RACT (Reactant or reagent); USES (Uses); NORL (No role in record)
RLD.NP Roles for non-specific derivatives from non-patents: ANST (Analytical study); BIOL (Biological study); FORM (Formation, nonpreparative); OCCU (Occurrence); PREP (Preparation); PROC (Process); PRP (Properties); RACT (Reactant or reagent); USES (Uses)

Absolute stereochemistry.

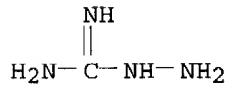


PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

3565 REFERENCES IN FILE CA (1907 TO DATE)
57 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
3571 REFERENCES IN FILE CAPLUS (1907 TO DATE)
69 REFERENCES IN FILE CAOLD (PRIOR TO 1967)

L86 ANSWER 13 OF 17 REGISTRY COPYRIGHT 2004 ACS on STN
RN 79-17-4 REGISTRY
CN Hydrazinecarboximidamide (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN Guanidine, amino- (8CI)
OTHER NAMES:
CN Aminate base
CN **Aminoguanidine**
CN Carbamimidic acid, hydrazide
CN Guanylhydrazine
CN Monoaminoguanidine
CN Pimagedine
FS 3D CONCORD
DR 10331-66-5, 146396-78-3
MF C H6 N4
CI COM
LC STN Files: ADISINSIGHT, ADISNEWS, AGRICOLA, ANABSTR, BEILSTEIN*, BIOBUSINESS, BIOSIS, BIOTECHNO, CA, CANCERLIT, CAOLD, CAPLUS, CASREACT, CBNB, CHEMCATS, CHEMINFORMRX, CHEMLIST, CIN, DDFU, DRUGU, EMBASE, GMELIN*, HODOC*, IFICDB, IFIPAT, IFIUDB, IMSDRUGNEWS, IMSRESEARCH, IPA, MEDLINE, MRCK*, NIOSHTIC, PHAR, PROMT, PROUSDDR, PS, RTECS*, SPECINFO, SYNTHLINE, TOXCENTER, USAN, USPAT2, USPATFULL, VETU
(*File contains numerically searchable property data)
Other Sources: EINECS**, WHO
(**Enter CHEMLIST File for up-to-date regulatory information)
DT.CA CAplus document type: Conference; Dissertation; Journal; Patent; Report
RL.P Roles from patents: ANST (Analytical study); BIOL (Biological study); OCCU (Occurrence); PREP (Preparation); PROC (Process); RACT (Reactant or reagent); USES (Uses); NORL (No role in record)
RLD.P Roles for non-specific derivatives from patents: ANST (Analytical

study); BIOL (Biological study); PREP (Preparation); PROC (Process); PRP (Properties); RACT (Reactant or reagent); USES (Uses)
RL.NP Roles from non-patents: ANST (Analytical study); BIOL (Biological study); CMBI (Combinatorial study); FORM (Formation, nonpreparative); OCCU (Occurrence); PREP (Preparation); PROC (Process); PRP (Properties); RACT (Reactant or reagent); USES (Uses); NORL (No role in record)
RLD.NP Roles for non-specific derivatives from non-patents: BIOL (Biological study); PREP (Preparation); PRP (Properties); RACT (Reactant or reagent); USES (Uses)



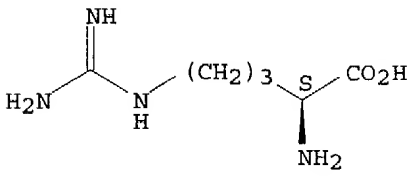
PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

1482 REFERENCES IN FILE CA (1907 TO DATE)
66 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
1484 REFERENCES IN FILE CAPLUS (1907 TO DATE)
14 REFERENCES IN FILE CAOLD (PRIOR TO 1967)

L86 ANSWER 14 OF 17 REGISTRY COPYRIGHT 2004 ACS on STN
RN 74-79-3 REGISTRY
CN L-Arginine (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN Arginine, L- (8CI)
OTHER NAMES:
CN (S)-2-Amino-5-[(aminoiminomethyl)amino]pentanoic acid
CN **Arginine**
CN L-(+)-Arginine
CN L-.alpha.-Amino-.delta.-guanidinovaleric acid
CN L-Arg
CN L-Norvaline, 5-[(aminoiminomethyl)amino]-
CN L-Ornithine, N5-(aminoiminomethyl)-
CN NSC 206269
CN Pentanoic acid, 2-amino-5-[(aminoiminomethyl)amino]-, (S)-
FS STEREOSEARCH
DR 667422-95-9, 7004-12-8, 142-49-4
MF C6 H14 N4 O2
CI COM
LC STN Files: ADISNEWS, AGRICOLA, ANABSTR, AQUIRE, BEILSTEIN*, BIOBUSINESS, BIOSIS, BIOTECHNO, CA, CABA, CANCERLIT, CAOLD, CAPLUS, CASREACT, CBNB, CEN, CHEMCATS, CHEMINFORMRX, CHEMLIST, CIN, CSCHEM, CSNB, DDFU, DETHERM*, DIOGENES, DRUGU, EMBASE, GMELIN*, HODOC*, HSDB*, IFICDB, IFIPAT, IFIUDB, IPA, MEDLINE, MRCK*, MSDS-OHS, NAPRALERT, NIOSHTIC, PHAR, PIRA, PROMT, PS, RTECS*, SPECINFO, SYNTHLINE, TOXCENTER, TULSA, USAN, USPAT2, USPATFULL, VETU
(*File contains numerically searchable property data)
Other Sources: DSL**, EINECS**, TSCA**, WHO
(**Enter CHEMLIST File for up-to-date regulatory information)
DT.CA CAplus document type: Book; Conference; Dissertation; Journal; Patent; Report
RL.P Roles from patents: ANST (Analytical study); BIOL (Biological study); CMBI (Combinatorial study); FORM (Formation, nonpreparative); MSC (Miscellaneous); OCCU (Occurrence); PREP (Preparation); PROC (Process); PRP (Properties); RACT (Reactant or reagent); USES (Uses); NORL (No role in record)
RLD.P Roles for non-specific derivatives from patents: ANST (Analytical study); BIOL (Biological study); FORM (Formation, nonpreparative); OCCU

(Occurrence); PREP (Preparation); PROC (Process); PRP (Properties); RACT (Reactant or reagent); USES (Uses)
RL.NP Roles from non-patents: ANST (Analytical study); BIOL (Biological study); CMBI (Combinatorial study); FORM (Formation, nonpreparative); MSC (Miscellaneous); OCCU (Occurrence); PREP (Preparation); PROC (Process); PRP (Properties); RACT (Reactant or reagent); USES (Uses); NORL (No role in record)
RLD.NP Roles for non-specific derivatives from non-patents: ANST (Analytical study); BIOL (Biological study); FORM (Formation, nonpreparative); MSC (Miscellaneous); OCCU (Occurrence); PREP (Preparation); PROC (Process); PRP (Properties); RACT (Reactant or reagent); USES (Uses)

Absolute stereochemistry.



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

38865 REFERENCES IN FILE CA (1907 TO DATE)
1084 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
38929 REFERENCES IN FILE CAPLUS (1907 TO DATE)
6 REFERENCES IN FILE CAOLD (PRIOR TO 1967)

L86 ANSWER 15 OF 17 REGISTRY COPYRIGHT 2004 ACS on STN
RN 70-54-2 REGISTRY
CN **Lysine (9CI)** (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN DL-Lysine
CN Lysine, DL- (8CI)
OTHER NAMES:
CN (.+-.)-2,6-Diaminohexanoic acid
CN (.+-.)-Lysine
CN (RS)-Lysine
CN 2,6-Diaminohexanoic acid
CN DL-.alpha.,.epsilon.-Diaminocaproic acid
FS 3D CONCORD
MF C6 H14 N2 O2
CI COM
LC STN Files: ADISNEWS, AGRICOLA, ANABSTR, AQUIRE, BEILSTEIN*, BIOBUSINESS, BIOSIS, BIOTECHNO, CA, CAOLD, CAPLUS, CASREACT, CEN, CHEMCATS, CHEMLIST, CIN, CSCHEM, DETHERM*, DIOGENES, EMBASE, GMELIN*, HODOC*, HSDB*, IFICDB, IFIPAT, IFIUDB, MEDLINE, NAPRALERT, PIRA, PROMT, TOXCENTER, TULSA, USPAT2, USPATFULL
(*File contains numerically searchable property data)
Other Sources: EINECS**
(**Enter CHEMLIST File for up-to-date regulatory information)
DT.CA CAplus document type: Conference; Dissertation; Journal; Patent; Report
RL.P Roles from patents: ANST (Analytical study); BIOL (Biological study); FORM (Formation, nonpreparative); PREP (Preparation); PROC (Process); PRP (Properties); RACT (Reactant or reagent); USES (Uses); NORL (No role in record)
RLD.P Roles for non-specific derivatives from patents: BIOL (Biological study); PREP (Preparation); PRP (Properties); RACT (Reactant or reagent); USES (Uses)
RL.NP Roles from non-patents: ANST (Analytical study); BIOL (Biological

study); FORM (Formation, nonpreparative); OCCU (Occurrence); PREP (Preparation); PROC (Process); PRP (Properties); RACT (Reactant or reagent); USES (Uses); NORL (No role in record)
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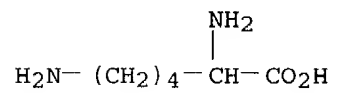


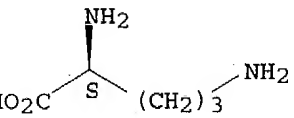
PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

637 REFERENCES IN FILE CA (1907 TO DATE)
26 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
637 REFERENCES IN FILE CAPLUS (1907 TO DATE)
1 REFERENCES IN FILE CAOLD (PRIOR TO 1967)

L86 ANSWER 16 OF 17 REGISTRY COPYRIGHT 2004 ACS on STN
RN 70-26-8 REGISTRY
CN L-Ornithine (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN Ornithine, L- (8CI)
OTHER NAMES:
CN (+)-S-Ornithine
CN (S)-.alpha.,.delta.-Diaminovaleric acid
CN (S)-2,5-Diaminopentanoic acid
CN (S)-Ornithine
CN L-(-)-Ornithine
CN L-Norvaline, 5-amino-
CN **Ornithine**
CN Pentanoic acid, 2,5-diamino-, (S)-
FS STEREOSEARCH
DR 7006-33-9, 410523-46-5
MF C5 H12 N2 O2
CI COM
LC STN Files: ADISNEWS, AGRICOLA, ANABSTR, BEILSTEIN*, BIOBUSINESS, BIOSIS, BIOTECHNO, CA, CABA, CANCERLIT, CAOLD, CAPLUS, CASREACT, CBNB, CHEMCATS, CHEMINFORMRX, CHEMLIST, CIN, CSCHEM, DDFU, DRUGU, EMBASE, GMELIN*, HODOC*, IFICDB, IFIPAT, IFIUDB, IPA, MEDLINE, MRCK*, NAPRALERT, NIOSHTIC, PIRA, PROMT, RTECS*, SYNTHLINE, TOXCENTER, TULSA, USAN, USPAT2, USPATFULL
(*File contains numerically searchable property data)
Other Sources: DSL**, EINECS**, TSCA**, WHO
(**Enter CHEMLIST File for up-to-date regulatory information)
DT.CA CAplus document type: Book; Conference; Dissertation; Journal; Patent; Report
RL.P Roles from patents: ANST (Analytical study); BIOL (Biological study); FORM (Formation, nonpreparative); OCCU (Occurrence); PREP (Preparation); PROC (Process); PRP (Properties); RACT (Reactant or reagent); USES (Uses); NORL (No role in record)
RLD.P Roles for non-specific derivatives from patents: ANST (Analytical study); BIOL (Biological study); FORM (Formation, nonpreparative); PREP (Preparation); PROC (Process); PRP (Properties); RACT (Reactant or reagent); USES (Uses)
RL.NP Roles from non-patents: ANST (Analytical study); BIOL (Biological study); CMBI (Combinatorial study); FORM (Formation, nonpreparative); MSC (Miscellaneous); OCCU (Occurrence); PREP (Preparation); PROC (Process); PRP (Properties); RACT (Reactant or reagent); USES (Uses);

NORL (No role in record)
LD.NP Roles for non-specific derivatives from non-patents: ANST (Analytical study); BIOL (Biological study); FORM (Formation, nonpreparative); OCCU (Occurrence); PREP (Preparation); PROC (Process); PRP (Properties); RACT (Reactant or reagent); USES (Uses)

bsolute stereochemistry.



*PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT**

7130 REFERENCES IN FILE CA (1907 TO DATE)
250 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
7141 REFERENCES IN FILE CAPLUS (1907 TO DATE)
4 REFERENCES IN FILE CAOLD (PRIOR TO 1967)

L86 ANSWER 17 OF 17 REGISTRY COPYRIGHT 2004 ACS on STN
RN 56-87-1 REGISTRY
CN L-Lysine (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN Lysine, L- (8CI)
OTHER NAMES:
CN (+)-S-Lysine
CN (S)-.alpha.,.epsilon.-Diaminocaproic acid
CN (S)-2,6-Diaminohexanoic acid
CN (S)-Lysine
CN .alpha.-Lysine
CN 2,6-Diaminohexanoic acid
CN Aminutrin
CN Aminutrin, 6-amino-
CN h-Lys-oh
CN Hexanoic acid, 2,6-diamino-, (S)-
CN L-(+)-Lysine
CN L-2,6-Diaminocaproic acid
CN L-Lys
CN L-Norleucine, 6-amino-
CN **Lysine**
CN Lysine acid
CS STEREOSEARCH
DR 6899-06-5, 48050-57-3, 280114-50-3
MF C6 H14 N2 O2
CI COM
LC STN Files: ADISNEWS, AGRICOLA, ANABSTR, BEILSTEIN*, BIOBUSINESS, BIOSIS, BIOTECHNO, CA, CABA, CANCERLIT, CAOLD, CAPLUS, CASREACT, CBNB, CEN, CHEMCATS, CHEMINFORMRX, CHEMLIST, CIN, CSCHEM, CSNB, DDFU, DETHERM*, DIOGENES, DIPPR*, DRUGU, EMBASE, GMELIN*, HODOC*, HSDB*, IFICDB, IFIPAT, IFIUDB, IPA, MEDLINE, MRCK*, MSDS-OHS, NAPRALERT, NIOSHTIC, PIRA, PROMT, PS, RTECS*, SPECINFO, SYNTHLINE, TOXCENTER, TULSA, USAN, USPAT2, USPATFULL, VETU, VTB
(*File contains numerically searchable property data)
Other Sources: DSL**, EINECS**, TSCA**, WHO
(**Enter CHEMLIST File for up-to-date regulatory information)
DT.CA CAplus document type: Book; Conference; Dissertation; Journal; Patent; Preprint; Report
RL.P Roles from patents: ANST (Analytical study); BIOL (Biological study); CMBI (Combinatorial study); FORM (Formation, nonpreparative); MSC

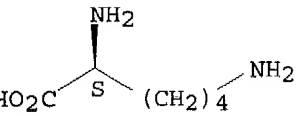
(Miscellaneous); OCCU (Occurrence); PREP (Preparation); PROC (Process); PRP (Properties); RACT (Reactant or reagent); USES (Uses); NORL (No role in record)

LD.P Roles for non-specific derivatives from patents: ANST (Analytical study); BIOL (Biological study); FORM (Formation, nonpreparative); OCCU (Occurrence); PREP (Preparation); PROC (Process); PRP (Properties); RACT (Reactant or reagent); USES (Uses)

RL.NP Roles from non-patents: ANST (Analytical study); BIOL (Biological study); CMBI (Combinatorial study); FORM (Formation, nonpreparative); MSC (Miscellaneous); OCCU (Occurrence); PREP (Preparation); PROC (Process); PRP (Properties); RACT (Reactant or reagent); USES (Uses); NORL (No role in record)

RLD.NP Roles for non-specific derivatives from non-patents: ANST (Analytical study); BIOL (Biological study); FORM (Formation, nonpreparative); MSC (Miscellaneous); OCCU (Occurrence); PREP (Preparation); PROC (Process); PRP (Properties); RACT (Reactant or reagent); USES (Uses)

Absolute stereochemistry.



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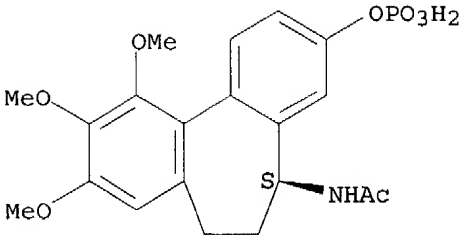
43181 REFERENCES IN FILE CA (1907 TO DATE)
1508 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
43241 REFERENCES IN FILE CAPLUS (1907 TO DATE)
7 REFERENCES IN FILE CAOLD (PRIOR TO 1967)

L87 ANSWER 1 OF 9 REGISTRY COPYRIGHT 2004 ACS on STN
RN 702694-01-7 REGISTRY
CN INDEX NAME NOT YET ASSIGNED
OTHER NAMES:
CN **N-Acetylcolchicinol dipotassium phosphate**
FS STEREOSEARCH
MF C20 H24 N O8 P . 2 K
SR CA
LC STN Files: CA, CAPLUS, TOXCENTER
DT.CA CAplus document type: Patent
RL.P Roles from patents: BIOL (Biological study); PREP (Preparation); USES (Uses)
CRN (219923-05-4)

Absolute stereochemistry.

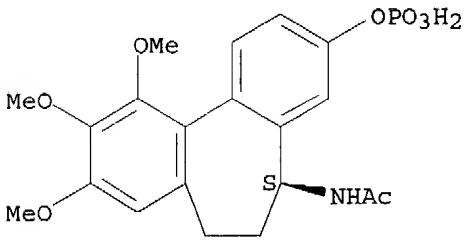


●2 K

1 REFERENCES IN FILE CA (1907 TO DATE)
1 REFERENCES IN FILE CAPLUS (1907 TO DATE)

L87 ANSWER 2 OF 9 REGISTRY COPYRIGHT 2004 ACS on STN
RN 702694-00-6 REGISTRY
CN INDEX NAME NOT YET ASSIGNED
OTHER NAMES:
CN **N-Acetylcolchicinol dilithium phosphate**
FS STEREOSEARCH
MF C20 H24 N O8 P . 2 Li
SR CA
LC STN Files: CA, CAPLUS, TOXCENTER
DT.CA CAplus document type: Patent
RL.P Roles from patents: BIOL (Biological study); PREP (Preparation); USES (Uses)
CRN (219923-05-4)

Absolute stereochemistry.



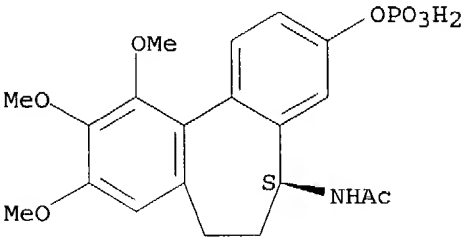
●2 Li

1 REFERENCES IN FILE CA (1907 TO DATE)
1 REFERENCES IN FILE CAPLUS (1907 TO DATE)

L87 ANSWER 3 OF 9 REGISTRY COPYRIGHT 2004 ACS on STN
RN 702693-99-0 REGISTRY
CN INDEX NAME NOT YET ASSIGNED
OTHER NAMES:
CN **N-Acetylcolchicinol disodium phosphate**
FS STEREOSEARCH
MF C20 H24 N O8 P . 2 Na
SR CA
LC STN Files: CA, CAPLUS, TOXCENTER

DT.CA CAplus document type: Patent
RL.P Roles from patents: BIOL (Biological study); PREP (Preparation); USES (Uses)
CRN (219923-05-4)

Absolute stereochemistry.

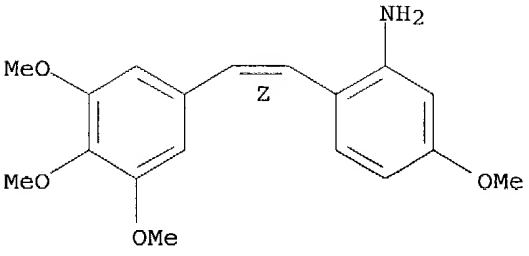


●2 Na

1 REFERENCES IN FILE CA (1907 TO DATE)
1 REFERENCES IN FILE CAPLUS (1907 TO DATE)

L87 ANSWER 4 OF 9 REGISTRY COPYRIGHT 2004 ACS on STN
RN 519060-26-5 REGISTRY
CN **Benzenamine, 5-methoxy-2-[(1Z)-2-(3,4,5-trimethoxyphenyl)ethenyl]-(9CI)** (CA INDEX NAME)
FS STEREOSEARCH
MF C18 H21 N O4
SR CA
LC STN Files: CA, CAPLUS, TOXCENTER, USPATFULL
DT.CA CAplus document type: Patent
RL.P Roles from patents: BIOL (Biological study); PREP (Preparation); USES (Uses)

Double bond geometry as shown.



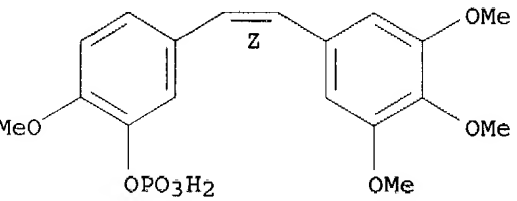
PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

1 REFERENCES IN FILE CA (1907 TO DATE)
1 REFERENCES IN FILE CAPLUS (1907 TO DATE)

L87 ANSWER 5 OF 9 REGISTRY COPYRIGHT 2004 ACS on STN
RN 222030-63-9 REGISTRY
CN Phenol, 2-methoxy-5-[(1Z)-2-(3,4,5-trimethoxyphenyl)ethenyl]-, dihydrogen phosphate (9CI) (CA INDEX NAME)
OTHER NAMES:
CN **Combretastatin A4 phosphate**

FS STEREOSEARCH
MF C18 H21 O8 P
CI COM
SR CA
LC STN Files: BIOSIS, CA, CAPLUS, CASREACT, EMBASE, IMSRESEARCH, PROUSDDR, TOXCENTER, USPAT2, USPATFULL
DT.CA CAplus document type: Conference; Journal; Patent
RL.P Roles from patents: BIOL (Biological study); PREP (Preparation); PROC (Process); PRP (Properties); RACT (Reactant or reagent); USES (Uses)
RL.NP Roles from non-patents: ANST (Analytical study); BIOL (Biological study); USES (Uses)

Double bond geometry as shown.

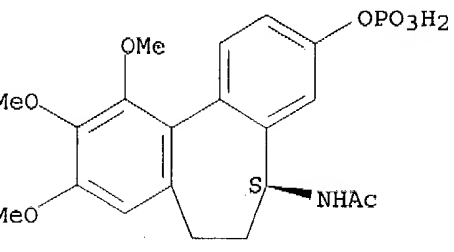


PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

39 REFERENCES IN FILE CA (1907 TO DATE)
39 REFERENCES IN FILE CAPLUS (1907 TO DATE)

L87 ANSWER 6 OF 9 REGISTRY COPYRIGHT 2004 ACS on STN
RN 219923-05-4 REGISTRY
CN Acetamide, N-[(5S)-6,7-dihydro-9,10,11-trimethoxy-3-(phosphonooxy)-5H-dibenzo[a,c]cyclohepten-5-yl]- (9CI) (CA INDEX NAME)
OTHER NAMES:
CN **N-Acetylcolchicinol dihydrogenphosphate**
CN ZD 6126
FS STEREOSEARCH
MF C20 H24 N O8 P
CI COM
SR CA
LC STN Files: BIOSIS, CA, CAPLUS, EMBASE, IMSRESEARCH, PROUSDDR, SYNTHLINE, TOXCENTER, USPATFULL
DT.CA CAplus document type: Journal; Patent
RL.P Roles from patents: BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)
RL.NP Roles from non-patents: BIOL (Biological study); PREP (Preparation); USES (Uses)

Absolute stereochemistry.

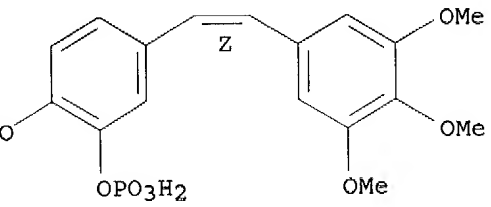


ROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT**

16 REFERENCES IN FILE CA (1907 TO DATE)
16 REFERENCES IN FILE CAPLUS (1907 TO DATE)

ANSWER 7 OF 9 REGISTRY COPYRIGHT 2004 ACS on STN
168555-66-6 REGISTRY
Phenol, 2-methoxy-5-[(1Z)-2-(3,4,5-trimethoxyphenyl)ethenyl]-, dihydrogen phosphate, disodium salt (9CI) (CA INDEX NAME)
IER CA INDEX NAMES:
Phenol, 2-methoxy-5-[2-(3,4,5-trimethoxyphenyl)ethenyl]-, dihydrogen phosphate, disodium salt, (Z)-
HER NAMES:
CA 4P
Combretastatin A4 disodium phosphate
STEREOSEARCH
229027-07-0
C18 H21 O8 P . 2 Na
CA
STN Files: BIOSIS, CA, CAPLUS, CASREACT, EMBASE, IMSDRUGNEWS, IMSRESEARCH, PROUSDDR, TOXCENTER, USPAT2, USPATFULL
CA CAplus document type: Dissertation; Journal; Patent
.P Roles from patents: BIOL (Biological study); PREP (Preparation); PROC (Process); PRP (Properties); RACT (Reactant or reagent); USES (Uses)
.NP Roles from non-patents: BIOL (Biological study); PREP (Preparation); PROC (Process); USES (Uses)
D.NP Roles for non-specific derivatives from non-patents: BIOL (Biological study); PREP (Preparation)
N (222030-63-9)

uble bond geometry as shown.



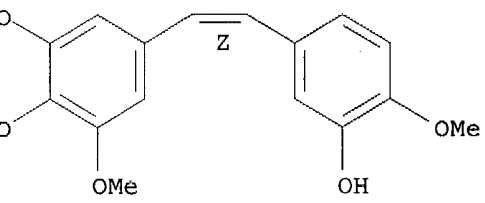
●2 Na

53 REFERENCES IN FILE CA (1907 TO DATE)
1 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
53 REFERENCES IN FILE CAPLUS (1907 TO DATE)

7 ANSWER 8 OF 9 REGISTRY COPYRIGHT 2004 ACS on STN
117048-59-6 REGISTRY
Phenol, 2-methoxy-5-[(1Z)-2-(3,4,5-trimethoxyphenyl)ethenyl]- (9CI) (CA INDEX NAME)
HER CA INDEX NAMES:
Phenol, 2-methoxy-5-[2-(3,4,5-trimethoxyphenyl)ethenyl]-, (Z)-
THER NAMES:
Combretastatin A4
CRC 87-09
NSC 817373
STEREOSEARCH

C18 H20 O5
COM
CA
STN Files: ADISINSIGHT, ADISNEWS, AGRICOLA, ANABSTR, BEILSTEIN*, BIOSIS, BIOTECHNO, CA, CANCERLIT, CAPLUS, CASREACT, CBNB, CHEMCATS, CIN, CSCHEM, DDFU, DRUGU, EMBASE, IMSDRUGNEWS, IMSRESEARCH, IPA, MEDLINE, MRCK*, PHAR, PROMT, TOXCENTER, USPAT2, USPATFULL
(*File contains numerically searchable property data)
.CA CAplus document type: Conference; Dissertation; Journal; Patent
.P Roles from patents: BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)
D.P Roles for non-specific derivatives from patents: BIOL (Biological study); PREP (Preparation); PRP (Properties); RACT (Reactant or reagent); USES (Uses)
.NP Roles from non-patents: ANST (Analytical study); BIOL (Biological study); MSC (Miscellaneous); OCCU (Occurrence); PREP (Preparation); PROC (Process); PRP (Properties); RACT (Reactant or reagent); USES (Uses)
D.NP Roles for non-specific derivatives from non-patents: BIOL (Biological study); PREP (Preparation); PROC (Process); PRP (Properties); USES (Uses)

uble bond geometry as shown.



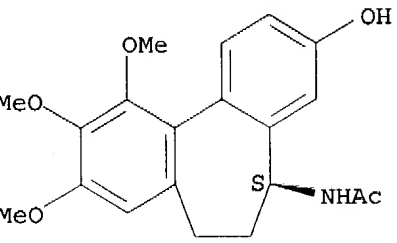
PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT**

175 REFERENCES IN FILE CA (1907 TO DATE)
16 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
177 REFERENCES IN FILE CAPLUS (1907 TO DATE)

7 ANSWER 9 OF 9 REGISTRY COPYRIGHT 2004 ACS on STN
38838-26-5 REGISTRY
Acetamide, N-[(5S)-6,7-dihydro-3-hydroxy-9,10,11-trimethoxy-5H-dibenzo[a,c]cyclohepten-5-yl]- (9CI) (CA INDEX NAME)
HER CA INDEX NAMES:
5H-Dibenzo[a,c]cycloheptene, acetamide deriv.
Acetamide, N-(6,7-dihydro-3-hydroxy-9,10,11-trimethoxy-5H-dibenzo[a,c]cyclohepten-5-yl)-, (S)-
Colchinol, acetyl- (6CI)
Colchinol, N-acetyl- (7CI)
HER NAMES:
N-Acetylcolchicinol
N-Acetylcolchinol
NSC 51045
STEREOSEARCH
C20 H23 N O5
COM
STN Files: BEILSTEIN*, BIOSIS, CA, CAOLD, CAPLUS, CHEMCATS, MEDLINE, PROUSDDR, RTECS*, TOXCENTER, USPATFULL
(*File contains numerically searchable property data)
.CA CAplus document type: Journal; Patent
.P Roles from patents: BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)

RL.NP Roles from non-patents: BIOL (Biological study); PREP (Preparation); PROC (Process); RACT (Reactant or reagent); USES (Uses); NORL (No role in record)

Absolute stereochemistry.



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

39 REFERENCES IN FILE CA (1907 TO DATE)
39 REFERENCES IN FILE CAPLUS (1907 TO DATE)
3 REFERENCES IN FILE CAOLD (PRIOR TO 1967)

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=> fil pascal jic biotechno esbio biotechds lifesci confsci dissabs toxcenter wpids
scisearch
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=> d que l85
L72       38460 SEA ((NITROGEN OR NITRIC)(W) OXIDE)(2A)(INHIB? OR ANTAGONI? OR
                BLOCK?)
L73       16468 SEA AMINOPYRIDINE OR AMINO(1W)(PYRIDINE OR METHYLPYRIDINE)
L74          66 SEA IMINOETHYLORNITHINE OR IMINOETHYLLYSINE OR IMINOETHYLYSINE
L75      313189 SEA THIOCITRULLINE OR HOMOTHIOCITRULLINE OR ARGININE
                OR ORNITHINE OR LYSINE OR CITRULLINE
L76       35184 SEA ALKYLTHIOUREA# OR THIOUREA# OR AMINOGUANIDINE OR
                AMINO GUANIDINE
L77        1701 SEA TUBULIN BIND?
L78         902 SEA COMBRETASTATIN#(W)(A4 OR A 4) OR ACETYLCOLCHINOL
                OR ACETYL COLCHINOL
L79       37277 SEA (NITROARGININE OR (METHYL OR NITRO OR AMINO))(1W)
                ARGININE OR METHYLARGININE OR AMINOARGININE
L81          57 SEA ((L72 OR L73 OR L74 OR L75 OR L76) OR L79) AND (L77 OR
                L78)
L83     3501987 SEA INTERACT? OR SYNERG? OR POTENTIAT? OR CONCURRENT? OR
                CODRUG# OR COADMIN? OR CO(W)(DRUG# OR ADMIN?)
L84      336957 SEA (THERAP? OR CHEMOTHERAP? OR DRUG#)(5A) COMB?
L85          29 SEA L81 AND ((L83 OR L84))
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. fil capl; d que 128;d que 133
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ILE COVERS 1907 - 13 Jul 2004  VOL 141 ISS 3
ILE LAST UPDATED: 12 Jul 2004  (20040712/ED)

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 substance identification.

OBI' IS DEFAULT SEARCH FIELD FOR 'CAPLUS' FILE


4           11 SEA FILE=REGISTRY ABB=ON  (10102-43-9/BI OR 156719-37-8/BI OR
               156719-38-9/BI OR 156719-41-4/BI OR 17035-90-4/BI OR 2149-70-4/
               BI OR 222030-63-9/BI OR 36889-13-1/BI OR 53774-63-3/BI OR
               57444-72-1/BI OR 695-34-1/BI)
9            1 SEA FILE=REGISTRY ABB=ON  "BENZENAMINE, 5-METHOXY-2-((1Z)-2-(3,
               4,5-TRIMETHOXYPHENYL)ETHENYL)-"/CN
10          10 SEA FILE=REGISTRY ABB=ON  L4 NOT P/ELS
11           1 SEA FILE=REGISTRY ABB=ON  NITRIC OXIDE/CN
12           9 SEA FILE=REGISTRY ABB=ON  L10 NOT L11
13           1 SEA FILE=REGISTRY ABB=ON  L-THIOCITRULLINE/CN
14           1 SEA FILE=REGISTRY ABB=ON  L-HOMOTHIOCITRULLINE/CN
15           2 SEA FILE=REGISTRY ABB=ON  ARGININE/CN
16           2 SEA FILE=REGISTRY ABB=ON  ORNITHINE/CN
17           2 SEA FILE=REGISTRY ABB=ON  LYSINE/CN
18           1 SEA FILE=REGISTRY ABB=ON  CITRULLINE/CN
19           1 SEA FILE=REGISTRY ABB=ON  AMINOGUANIDINE/CN
20           3 SEA FILE=REGISTRY ABB=ON  COMBRETASTATIN A4?/CN
21           5 SEA FILE=REGISTRY ABB=ON  N-ACETYLCOLCHICINOL?/CN
23           1 SEA FILE=REGISTRY ABB=ON  NITRIC OXIDE SYNTHASE/CN
24       10512 SEA FILE=CAPLUS ABB=ON  (L11 OR L23 OR (NITROGEN/OBI OR
               NITRIC/OBI)(W)OXIDE/OBI)(L)(INHIB?/OBI OR ANTAG?/OBI OR
               BLOCK?/OBI)
25       72428 SEA FILE=CAPLUS ABB=ON  (L12 OR L13 OR L14 OR L15 OR L16 OR
               L17 OR L18 OR L19)
26         282 SEA FILE=CAPLUS ABB=ON  L20 OR L21 OR L9
28           7 SEA FILE=CAPLUS ABB=ON  (L26) AND (L24 OR L25)



4           11 SEA FILE=REGISTRY ABB=ON  (10102-43-9/BI OR 156719-37-8/BI OR
               156719-38-9/BI OR 156719-41-4/BI OR 17035-90-4/BI OR 2149-70-4/
               BI OR 222030-63-9/BI OR 36889-13-1/BI OR 53774-63-3/BI OR
               57444-72-1/BI OR 695-34-1/BI)
9            1 SEA FILE=REGISTRY ABB=ON  "BENZENAMINE, 5-METHOXY-2-((1Z)-2-(3,
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L10          10 SEA FILE=REGISTRY ABB=ON  L4 NOT P/ELS
L11           1 SEA FILE=REGISTRY ABB=ON  NITRIC OXIDE/CN
L12           9 SEA FILE=REGISTRY ABB=ON  L10 NOT L11
L13           1 SEA FILE=REGISTRY ABB=ON  L-THIOCITRULLINE/CN
L14           1 SEA FILE=REGISTRY ABB=ON  L-HOMOTHIOCITRULLINE/CN
L15           2 SEA FILE=REGISTRY ABB=ON  ARGININE/CN
L16           2 SEA FILE=REGISTRY ABB=ON  ORNITHINE/CN
L17           2 SEA FILE=REGISTRY ABB=ON  LYSINE/CN
L18           1 SEA FILE=REGISTRY ABB=ON  CITRULLINE/CN
L19           1 SEA FILE=REGISTRY ABB=ON  AMINOGUANIDINE/CN
L20           3 SEA FILE=REGISTRY ABB=ON  COMBRETASTATIN A4?/CN
L21           5 SEA FILE=REGISTRY ABB=ON  N-ACETYLCOLCHICINOL?/CN
L22        1060 SEA FILE=CAPLUS ABB=ON  TUBULIN#/OBI(3A)BIND?/OBI
L23           1 SEA FILE=REGISTRY ABB=ON  NITRIC OXIDE SYNTHASE/CN
L24       10512 SEA FILE=CAPLUS ABB=ON  (L11 OR L23 OR (NITROGEN/OBI OR
                NITRIC/OBI)(W)OXIDE/OBI)(L)(INHIB?/OBI OR ANTAG?/OBI OR
                BLOCK?/OBI)
L25       72428 SEA FILE=CAPLUS ABB=ON  (L12 OR L13 OR L14 OR L15 OR L16 OR
                L17 OR L18 OR L19)
L26         282 SEA FILE=CAPLUS ABB=ON  L20 OR L21 OR L9
L32       33604 SEA FILE=CAPLUS ABB=ON  DRUG INTERACTIONS+OLD,NT/CT OR DRUG
                DELIVERY SYSTEMS+OLD/CT(L)COMB?/OBI
L33           2 SEA FILE=CAPLUS ABB=ON  (L22 OR L26) AND (L24 OR L25) AND L32


=> s l28 or l33
L88           7 L28 OR L33

=> fil uspatf; d que l38; fil medl; d que l49
FILE 'USPATFULL' ENTERED AT 15:45:27 ON 13 JUL 2004
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FILE COVERS 1971 TO PATENT PUBLICATION DATE: 13 Jul 2004 (20040713/PD)
FILE LAST UPDATED: 13 Jul 2004 (20040713/ED)
HIGHEST GRANTED PATENT NUMBER: US2004126357
HIGHEST APPLICATION PUBLICATION NUMBER: US2004133957
CA INDEXING IS CURRENT THROUGH 13 Jul 2004 (20040713/UPCA)
ISSUE CLASS FIELDS (/INCL) CURRENT THROUGH: 13 Jul 2004 (20040713/PD)
REVISED CLASS FIELDS (/NCL) LAST RELOADED: Jun 2004
USPTO MANUAL OF CLASSIFICATIONS THESAURUS ISSUE DATE: Jun 2004

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>>>  original, i.e., the earliest published granted patents or         <<<
>>>  applications.  USPAT2 contains full text of the latest US         <<<
>>>  publications, starting in 2001, for the inventions covered in     <<<
>>>  USPATFULL.  A USPATFULL record contains not only the original     <<<
>>>  published document but also a list of any subsequent              <<<
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>>>  publication date for all the US publications for an invention     <<<
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>>>  classifications, or claims, that may potentially change from      <<<
>>>  the earliest to the latest publication.                           <<<

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L4          11 SEA FILE=REGISTRY ABB=ON  (10102-43-9/BI OR 156719-37-8/BI OR
               156719-38-9/BI OR 156719-41-4/BI OR 17035-90-4/BI OR 2149-70-4/
               BI OR 222030-63-9/BI OR 36889-13-1/BI OR 53774-63-3/BI OR
               57444-72-1/BI OR 695-34-1/BI)
L9           1 SEA FILE=REGISTRY ABB=ON  "BENZENAMINE, 5-METHOXY-2-((1Z)-2-(3,
               4,5-TRIMETHOXYPHENYL)ETHENYL)-"/CN
L10         10 SEA FILE=REGISTRY ABB=ON  L4 NOT P/ELS
L11          1 SEA FILE=REGISTRY ABB=ON  NITRIC OXIDE/CN
L12          9 SEA FILE=REGISTRY ABB=ON  L10 NOT L11
L13          1 SEA FILE=REGISTRY ABB=ON  L-THIOCITRULLINE/CN
L14          1 SEA FILE=REGISTRY ABB=ON  L-HOMOTHIOCITRULLINE/CN
L15          2 SEA FILE=REGISTRY ABB=ON  ARGININE/CN
L16          2 SEA FILE=REGISTRY ABB=ON  ORNITHINE/CN
L17          2 SEA FILE=REGISTRY ABB=ON  LYSINE/CN
L18          1 SEA FILE=REGISTRY ABB=ON  CITRULLINE/CN
L19          1 SEA FILE=REGISTRY ABB=ON  AMINOGUANIDINE/CN
L20          3 SEA FILE=REGISTRY ABB=ON  COMBRETASTATIN A4?/CN
L21          5 SEA FILE=REGISTRY ABB=ON  N-ACETYLCOLCHICINOL?/CN
L23          1 SEA FILE=REGISTRY ABB=ON  NITRIC OXIDE SYNTHASE/CN
L34        713 SEA FILE=USPATFULL ABB=ON  (L11 OR L23 OR ((NITRIC OR NITROGEN)
               (W)OXIDE)/IT)(L)(INHIB? OR ANTAG? OR BLOCK?)/IT
L35       3964 SEA FILE=USPATFULL ABB=ON  (L12 OR L13 OR L14 OR L15 OR L16 OR
               L17 OR L18 OR L19)
L36         51 SEA FILE=USPATFULL ABB=ON  (TUBULIN#(3A)BIND?)/IT,TI,AB,CLM
L37         62 SEA FILE=USPATFULL ABB=ON  L9 OR (L20 OR L21)
L38          1 SEA FILE=USPATFULL ABB=ON  (L34 OR L35) AND (L36 OR L37)


FILE 'MEDLINE' ENTERED AT 15:45:27 ON 13 JUL 2004

 FILE LAST UPDATED: 10 JUL 2004 (20040710/UP). FILE COVERS 1951 TO DATE.

 On February 29, 2004, the 2004 MeSH terms were loaded. See HELP RLOAD
 for details. OLDMEDLINE now back to 1951.

 MEDLINE thesauri in the /CN, /CT, and /MN fields incorporate the
 MeSH 2004 vocabulary. See http://www.nlm.nih.gov/mesh/ and
 http://www.nlm.nih.gov/pubs/techbull/nd03/nd03_mesh.html for a
 description of changes.

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 substance identification.


L4          11 SEA FILE=REGISTRY ABB=ON  (10102-43-9/BI OR 156719-37-8/BI OR
               156719-38-9/BI OR 156719-41-4/BI OR 17035-90-4/BI OR 2149-70-4/
               BI OR 222030-63-9/BI OR 36889-13-1/BI OR 53774-63-3/BI OR
               57444-72-1/BI OR 695-34-1/BI)
L9           1 SEA FILE=REGISTRY ABB=ON  "BENZENAMINE, 5-METHOXY-2-((1Z)-2-(3,
               4,5-TRIMETHOXYPHENYL)ETHENYL)-"/CN
L10         10 SEA FILE=REGISTRY ABB=ON  L4 NOT P/ELS
L11          1 SEA FILE=REGISTRY ABB=ON  NITRIC OXIDE/CN
L12          9 SEA FILE=REGISTRY ABB=ON  L10 NOT L11
L13          1 SEA FILE=REGISTRY ABB=ON  L-THIOCITRULLINE/CN
L14          1 SEA FILE=REGISTRY ABB=ON  L-HOMOTHIOCITRULLINE/CN
L15          2 SEA FILE=REGISTRY ABB=ON  ARGININE/CN
L16          2 SEA FILE=REGISTRY ABB=ON  ORNITHINE/CN
L17          2 SEA FILE=REGISTRY ABB=ON  LYSINE/CN
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L18           1 SEA FILE=REGISTRY ABB=ON  CITRULLINE/CN
L19           1 SEA FILE=REGISTRY ABB=ON  AMINOGUANIDINE/CN
L20           3 SEA FILE=REGISTRY ABB=ON  COMBRETASTATIN A4?/CN
L21           5 SEA FILE=REGISTRY ABB=ON  N-ACETYLCOLCHICINOL?/CN
L39        7734 SEA FILE=MEDLINE ABB=ON  NITRIC-OXIDE SYNTHASE/CT(L)AI/CT
L40        2576 SEA FILE=MEDLINE ABB=ON  NITRIC OXIDE/CT(L)AI/CT
L41       50385 SEA FILE=MEDLINE ABB=ON  (L12 OR L13 OR L14 OR L15 OR L16 OR
                 L17 OR L18 OR L19)
L43        1371 SEA FILE=MEDLINE ABB=ON  TUBULIN#(3A)BIND?
L44         108 SEA FILE=MEDLINE ABB=ON  L9 OR (L20 OR L21)
L45         173 SEA FILE=MEDLINE ABB=ON  COMBRETASTATIN#(W)(A 4 OR A4) OR
                 ACETYLCOLCHINOL#
L47        2441 SEA FILE=MEDLINE ABB=ON  ANGIOGENESIS INHIBITORS/CT
L48      203563 SEA FILE=MEDLINE ABB=ON  DRUG INTERACTIONS+NT/CT OR DRUG
                 COMBINATIONS/CT OR DRUG THERAPY, COMBINATION/CT
L49           3 SEA FILE=MEDLINE ABB=ON  (L39 OR L40 OR L41) AND (L43 OR L44
                 OR L45) AND (L47 OR L48)


=> fil embase; d que l57; fil biosis; d que l64; fil drugu; d que l71
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L4           11 SEA FILE=REGISTRY ABB=ON  (10102-43-9/BI OR 156719-37-8/BI OR
                 156719-38-9/BI OR 156719-41-4/BI OR 17035-90-4/BI OR 2149-70-4/
                 BI OR 222030-63-9/BI OR 36889-13-1/BI OR 53774-63-3/BI OR
                 57444-72-1/BI OR 695-34-1/BI)
L9            1 SEA FILE=REGISTRY ABB=ON  "BENZENAMINE, 5-METHOXY-2-((1Z)-2-(3,
                 4,5-TRIMETHOXYPHENYL)ETHENYL)-"/CN
L10          10 SEA FILE=REGISTRY ABB=ON  L4 NOT P/ELS
L11           1 SEA FILE=REGISTRY ABB=ON  NITRIC OXIDE/CN
L12           9 SEA FILE=REGISTRY ABB=ON  L10 NOT L11
L13           1 SEA FILE=REGISTRY ABB=ON  L-THIOCITRULLINE/CN
L14           1 SEA FILE=REGISTRY ABB=ON  L-HOMOTHIOCITRULLINE/CN
L15           2 SEA FILE=REGISTRY ABB=ON  ARGININE/CN
L16           2 SEA FILE=REGISTRY ABB=ON  ORNITHINE/CN
L17           2 SEA FILE=REGISTRY ABB=ON  LYSINE/CN
L18           1 SEA FILE=REGISTRY ABB=ON  CITRULLINE/CN
L19           1 SEA FILE=REGISTRY ABB=ON  AMINOGUANIDINE/CN
L20           3 SEA FILE=REGISTRY ABB=ON  COMBRETASTATIN A4?/CN
L21           5 SEA FILE=REGISTRY ABB=ON  N-ACETYLCOLCHICINOL?/CN
L50       40590 SEA FILE=EMBASE ABB=ON  (L12 OR L13 OR L14 OR L15 OR L16 OR
                 L17 OR L18 OR L19)
L51        6565 SEA FILE=EMBASE ABB=ON  NITRIC OXIDE SYNTHASE INHIBITOR/CT
L52       43922 SEA FILE=EMBASE ABB=ON  NITRIC OXIDE/CT
L53         194 SEA FILE=EMBASE ABB=ON  L9 OR (L20 OR L21)
L54          19 SEA FILE=EMBASE ABB=ON  N ACETYLCOLCHINOL PHOSPHATE/CT OR N
                 ACETYLCOLCHINOL/CT
L55         176 SEA FILE=EMBASE ABB=ON  COMBRETASTATIN A4/CT
L56           2 SEA FILE=EMBASE ABB=ON  TUBULIN BINDING AGENT/CT
L57           8 SEA FILE=EMBASE ABB=ON  (L50 OR L51 OR L52) AND (L53 OR L54 OR
                 L55 OR L56)
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FROM JANUARY 1969 TO DATE.

RECORDS LAST ADDED: 7 July 2004 (20040707/ED)

FILE RELOADED: 19 October 2003.


L4            11 SEA FILE=REGISTRY ABB=ON  (10102-43-9/BI OR 156719-37-8/BI OR
                 156719-38-9/BI OR 156719-41-4/BI OR 17035-90-4/BI OR 2149-70-4/
                 BI OR 222030-63-9/BI OR 36889-13-1/BI OR 53774-63-3/BI OR
                 57444-72-1/BI OR 695-34-1/BI)
L9             1 SEA FILE=REGISTRY ABB=ON  "BENZENAMINE, 5-METHOXY-2-((1Z)-2-(3,
                 4,5-TRIMETHOXYPHENYL)ETHENYL)-"/CN
L10           10 SEA FILE=REGISTRY ABB=ON  L4 NOT P/ELS
L11            1 SEA FILE=REGISTRY ABB=ON  NITRIC OXIDE/CN
L12            9 SEA FILE=REGISTRY ABB=ON  L10 NOT L11
L13            1 SEA FILE=REGISTRY ABB=ON  L-THIOCITRULLINE/CN
L14            1 SEA FILE=REGISTRY ABB=ON  L-HOMOTHIOCITRULLINE/CN
L15            2 SEA FILE=REGISTRY ABB=ON  ARGININE/CN
L16            2 SEA FILE=REGISTRY ABB=ON  ORNITHINE/CN
L17            2 SEA FILE=REGISTRY ABB=ON  LYSINE/CN
L18            1 SEA FILE=REGISTRY ABB=ON  CITRULLINE/CN
L19            1 SEA FILE=REGISTRY ABB=ON  AMINOGUANIDINE/CN
L20            3 SEA FILE=REGISTRY ABB=ON  COMBRETASTATIN A4?/CN
L21            5 SEA FILE=REGISTRY ABB=ON  N-ACETYLCOLCHICINOL?/CN
L58        43595 SEA FILE=BIOSIS ABB=ON  (L12 OR L13 OR L14 OR L15 OR L16 OR
                 L17 OR L18 OR L19)
L59        15292 SEA FILE=BIOSIS ABB=ON  ((NITROGEN OR NITRIC)(W)OXIDE)(2A)(INHI
                 B? OR ANTAGONI? OR BLOCK?)
L60          134 SEA FILE=BIOSIS ABB=ON  L9 OR L21 OR L20
L61          235 SEA FILE=BIOSIS ABB=ON  COMBRETASTATIN#(W)(A4 OR A 4) OR
                 ACETYLCOLCHINOL OR ACETYL COLCHINOL
L64            6 SEA FILE=BIOSIS ABB=ON  (L58 OR L59) AND (L60 OR L61)



FILE 'DRUGU' ENTERED AT 15:45:42 ON 13 JUL 2004
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FILE LAST UPDATED: 7 JUL 2004       <20040707/UP>
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>>>  A RECENT REVIEW OF PSYCHIATRIC DISEASE KEYWORDS USED
     IN DERWENT DRUG FILE HAS PROMPTED A REVISION BASED
     ON STANDARD TERMS USED IN DSM-IV (DIAGNOSTIC AND
     STATISTICAL MANUAL OF MENTAL DISORDERS - FOURTH
     EDITION).
     FOR FURTHER DETAILS:
http://thomsonderwent.com/derwenthome/support/userguides/lit_guide



L4            11 SEA FILE=REGISTRY ABB=ON  (10102-43-9/BI OR 156719-37-8/BI OR
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          156719-38-9/BI OR 156719-41-4/BI OR 17035-90-4/BI OR 2149-70-4/
          BI OR 222030-63-9/BI OR 36889-13-1/BI OR 53774-63-3/BI OR
          57444-72-1/BI OR 695-34-1/BI)
        1 SEA FILE=REGISTRY ABB=ON  "BENZENAMINE, 5-METHOXY-2-((1Z)-2-(3,
          4,5-TRIMETHOXYPHENYL)ETHENYL)-"/CN
       10 SEA FILE=REGISTRY ABB=ON  L4 NOT P/ELS
        1 SEA FILE=REGISTRY ABB=ON  NITRIC OXIDE/CN
        9 SEA FILE=REGISTRY ABB=ON  L10 NOT L11
        1 SEA FILE=REGISTRY ABB=ON  L-THIOCITRULLINE/CN
        1 SEA FILE=REGISTRY ABB=ON  L-HOMOTHIOCITRULLINE/CN
        2 SEA FILE=REGISTRY ABB=ON  ARGININE/CN
        2 SEA FILE=REGISTRY ABB=ON  ORNITHINE/CN
        2 SEA FILE=REGISTRY ABB=ON  LYSINE/CN
        1 SEA FILE=REGISTRY ABB=ON  CITRULLINE/CN
        1 SEA FILE=REGISTRY ABB=ON  AMINOGUANIDINE/CN
        3 SEA FILE=REGISTRY ABB=ON  COMBRETASTATIN A4?/CN
        5 SEA FILE=REGISTRY ABB=ON  N-ACETYLCOLCHICINOL?/CN
     1203 SEA FILE=DRUGU ABB=ON  (L12 OR L13 OR L14 OR L15 OR L16 OR L17
          OR L18 OR L19)
     3713 SEA FILE=DRUGU ABB=ON  ((NITROGEN OR NITRIC)(W)OXIDE)(2A)(INHIB
          ? OR ANTAGONI? OR BLOCK?)
      102 SEA FILE=DRUGU ABB=ON  L9 OR (L20 OR L21)
      243 SEA FILE=DRUGU ABB=ON  COMBRETASTATIN#(W)(A4 OR A 4) OR
          ACETYLCOLCHINOL OR ACETYL COLCHINOL
      204 SEA FILE=DRUGU ABB=ON  TUBULIN# BINDING
        4 SEA FILE=DRUGU ABB=ON  (L66 OR L67) AND (L68 OR L69 OR L70)


 dup rem l49,l71,l88,l64,l57,l85,l38
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ROCESSING COMPLETED FOR L71
ROCESSING COMPLETED FOR L88
ROCESSING COMPLETED FOR L64
ROCESSING COMPLETED FOR L57
ROCESSING COMPLETED FOR L85
ROCESSING COMPLETED FOR L38
39 27 DUP REM L49 L71 L88 L64 L57 L85 L38 (31 DUPLICATES REMOVED)
ANSWERS '1-3' FROM FILE MEDLINE
ANSWERS '4-7' FROM FILE DRUGU
ANSWERS '8-11' FROM FILE CAPLUS
ANSWERS '12-13' FROM FILE BIOSIS
ANSWERS '14-19' FROM FILE EMBASE
ANSWERS '20-21' FROM FILE BIOTECHNO
ANSWERS '22-24' FROM FILE TOXCENTER
ANSWER '25' FROM FILE WPIDS
ANSWER '26' FROM FILE SCISEARCH
ANSWER '27' FROM FILE USPATFULL

> d iall 1-7; d ibib ed ab hitrn 8-11; d iall 12-26; d ibib ab hitrn 27; fil hom

39 ANSWER 1 OF 27 MEDLINE on STN DUPLICATE 5
CCESSION NUMBER: 2002698171 MEDLINE
OCUMENT NUMBER: PubMed ID: 12459382
ITLE: Enhancement of vascular targeting by inhibitors of nitric oxide synthase.
UTHOR: Davis Peter D; Tozer Gillian M; Naylor Matthew A; Thomson Peter; Lewis Gemma; Hill Sally A
ORPORATE SOURCE: Angiogene Pharmaceuticals Ltd., England, Oxford, UK.. pdd@angiogene.co.uk
OURCE: International journal of radiation oncology, biology, physics, (2002 Dec 1) 54 (5) 1532-6. Journal code: 7603616. ISSN: 0360-3016.
UB. COUNTRY: United States
OCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
ANGUAGE: English
ILE SEGMENT: Priority Journals
NTRY MONTH: 200301
NTRY DATE: Entered STN: 20021217
Last Updated on STN: 20030103
Entered Medline: 20030102

BSTRACT:
URPOSE: This study investigates the enhancement of the vascular targeting ctivity of the **tubulin-binding** agent **combretastatin*** **A4** phosphate (CA4P) by various inhibitors of itric oxide synthases. METHODS AND MATERIALS: The syngeneic tumors CaNT and aS growing in CBA mice were used for this study. Reduction in perfused ascular volume was measured by injection of Hoechst 33342 24 h after drug dministration. Necrosis (hematoxylin and eosin stain) was assessed also at 24 after treatment. **Combretastatin A4** phosphate was ynthesized by a modification of the published procedure and the nitric oxide ynthase inhibitors L-NNA, L-NMMA, L-NIO, L-NIL, S-MTC, S-EIT, AMP, AMT, and

TC, obtained from commercial sources. RESULTS: A statistically significant gmentation of the reduction in perfused vascular volume by CA4P in the CaNT mor was observed with L-NNA, AMP, and AMT. An increase in CA4P-induced crosis in the same tumor achieved significance with L-NNA, L-NMMA, L-NIL, and T. CA4P induced little necrosis in the SaS tumor, but combination with the nibitors L-NNA, L-NMMA, L-NIO, S-EIT, and L-TC was effective. CONCLUSIONS: gmentation of CA4P activity by nitric oxide synthase inhibitors of different ructural classes supports a nitric oxide-related mechanism for this effect. NNA was the most effective inhibitor studied.

NTROLLED TERM: ***Angiogenesis Inhibitors: TU, therapeutic use**
Animals
*Antineoplastic Agents, Phytogenic: TU, therapeutic use
Benzimidazoles: PD, pharmacology
*Enzyme Inhibitors: PD, pharmacology
Fluorescent Dyes: PD, pharmacology
Mice
Mice, Inbred CBA
Models, Chemical
Necrosis
*Neovascularization, Pathologic
***Nitric-Oxide Synthase: AI, antagonists & inhibitors**
*Stilbenes: TU, therapeutic use
Time Factors
Tubulin: ME, metabolism
Tumor Cells, Cultured

S REGISTRY NO.: **117048-59-6 (combretastatin A-4)**; 23491-52-3 (HOE 33342)

EMICAL NAME: 0 (Angiogenesis Inhibitors); 0 (Antineoplastic Agents, Phytogenic); 0 (Benzimidazoles); 0 (Enzyme Inhibitors); 0 (Fluorescent Dyes); 0 (Stilbenes); 0 (Tubulin); EC 1.14.13.39 (Nitric-Oxide Synthase)

9 ANSWER 2 OF 27 MEDLINE on STN DUPLICATE 7

CESSION NUMBER: 2001482503 MEDLINE

CUMENT NUMBER: PubMed ID: 11522635

TLE: Mechanisms associated with tumor vascular shut-down induced by **combretastatin A-4** phosphate: intravital microscopy and measurement of vascular permeability.

THOR: Tozer G M; Prise V E; Wilson J; Cemazar M; Shan S; Dewhirst M W; Barber P R; Vojnovic B; Chaplin D J

RPORATE SOURCE: Gray Cancer Institute, Mount Vernon Hospital, Northwood, Middlesex, HA6 2JR, United Kingdom.. tozer@graylab.ac.uk

URCE: Cancer research, (2001 Sep 1) 61 (17) 6413-22. Journal code: 2984705R. ISSN: 0008-5472.

B. COUNTRY: United States

CUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)

NGUAGE: English

LE SEGMENT: Priority Journals

TRY MONTH: 200109

TRY DATE: Entered STN: 20010830
Last Updated on STN: 20010917
Entered Medline: 20010913

STRACT:

e tumor vascular effects of the tubulin destabilizing agent disodium mbretastatinA-4 3-O-phosphate (CA-4-P) were investigated in the rat P22 tumor owing in a dorsal skin flap window chamber implanted into BD9 rats. CA-4-P in clinical trial as a tumor vascular targeting agent. In animal tumors, it n cause the shut-down of blood flow, leading to extensive tumor cell crosis. However, the mechanisms leading to vascular shut-down are still known. Tumor vascular effects were visualized and monitored on-line before

d after the administration of two doses of CA-4-P (30 and 100 mg/kg) using travital microscopy. The combined effect of CA-4-P and systemic nitric oxide nthase (NOS) inhibition using N(omega)-nitro-L-arginine (L-NNA) was also sessed, because this combination has been shown previously to have a tentiating effect. The early effect of CA-4-P on tumor vascular permeability albumin was determined to assess whether this could be involved in the chanism of action of the drug. Tumor blood flow reduction was extremely pid after CA-4-P treatment, with red cell velocity decreasing throughout the servation period and dropping to <5% of the starting value by 1 h. NOS hibition alone caused a 50% decrease in red cell velocity, and the combined eatment of CA-4-P and NOS inhibition was approximately additive. The chanism of blood flow reduction was very different for NOS inhibition and -4-P. That of NOS inhibition could be explained by a decrease in vessel ameter, which was most profound on the arteriolar side of the tumor rculation. In contrast, the effects of CA-4-P resembled an acute flammatory reaction resulting in a visible loss of a large proportion of the allest blood vessels. There was some return of visible vasculature at 1 h ter treatment, but the blood in these vessels was static or nearly so, and ny of the vessels were distended. The hematocrit within larger draining mor venules tended to increase at early times after CA-4-P, suggesting fluid ss from the blood. The stacking of red cells to form rouleaux was also a mmon feature, coincident with slowing of blood flow; and these two factors uld lead to an increase in viscous resistance to blood flow. Tumor vascular rmeability to albumin was increased to approximately 160% of control values 1 and 10 min after treatment. This could lead to an early decrease in tumor ood flow via an imbalance between intravascular and tissue pressures and/or increase in blood viscosity as a result of increased hematocrit. These sults suggest a mechanism of action of CA-4-P in vivo. Combination of CA-4-P th a NOS inhibitor has an additive effect, which it may be possible to ploit therapeutically.

ONTROLLED TERM: Check Tags: Male; Support, Non-U.S. Gov't
***Angiogenesis Inhibitors: PD, pharmacology**
Animals
*Antineoplastic Agents, Phytogenic: PD, pharmacology
Capillary Permeability: DE, drug effects
*Carcinosarcoma: BS, blood supply
Carcinosarcoma: DT, drug therapy
Carcinosarcoma: ME, metabolism
Drug Synergism
Enzyme Inhibitors: PD, pharmacology
Microscopy, Fluorescence: MT, methods
*Neoplasms, Experimental: BS, blood supply
Neoplasms, Experimental: DT, drug therapy
Neoplasms, Experimental: ME, metabolism
*Neovascularization, Pathologic: DT, drug therapy
Neovascularization, Pathologic: PP, physiopathology
Nitric Oxide: BI, biosynthesis
Nitric Oxide: PH, physiology
Nitric-Oxide Synthase: AI, antagonists & inhibitors
Nitroarginine: PD, pharmacology
Rats
*Stilbenes: PD, pharmacology

AS REGISTRY NO.: 10102-43-9 (Nitric Oxide); **117048-59-6 (combretastatin A-4); 2149-70-4 (Nitroarginine)**

HEMICAL NAME: 0 (Angiogenesis Inhibitors); 0 (Antineoplastic Agents, Phytogenic); 0 (Enzyme Inhibitors); 0 (Stilbenes); EC 1.14.13.39 (Nitric-Oxide Synthase)

39 ANSWER 3 OF 27 MEDLINE on STN
CCESSION NUMBER: 2003466591 MEDLINE
OCUMENT NUMBER: PubMed ID: 14528278

TITLE: Ocular neovascularization: a valuable model system.
AUTHOR: Campochiaro Peter Anthony; Hackett Sean Francis
CORPORATE SOURCE: Department of Ophthalmology, The Johns Hopkins University School of Medicine, Maumenee 719, 600 N. Wolfe Street, Baltimore, MD 21287-9277, USA.. pcampo@inmi.edu
CONTRACT NUMBER: EY05951 (NEI)
EY12609 (NEI)
P30EY1765 (NEI)
SOURCE: Oncogene, (2003 Sep 29) 22 (42) 6537-48. Ref: 133
Journal code: 8711562. ISSN: 0950-9232.
PUB. COUNTRY: England: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, ACADEMIC)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200311
ENTRY DATE: Entered STN: 20031008
Last Updated on STN: 20031113
Entered Medline: 20031112

ABSTRACT:
There is no unique formula for angiogenesis. Instead there is a large group of potential participating proteins that interact in complex ways. Depending upon the surrounding cell types and the relative expression levels of angiogenesis-related proteins, the 'angiogenesis cascade' can vary. Therefore, it is valuable to study and compare the role of proteins in several well-characterized vascular beds. The eye provides a useful model system, because it contains several vascular beds sandwiched between avascular tissue. This allows for unequivocal identification and quantitation of new vessels. Retina-specific promoters combined with inducible promoter systems provide a means to regulate the expression of proteins of interest. As a relatively isolated compartment, the eye also provides advantages for gene transfer. By gaining insight regarding the molecular signals involved in various types of ocular angiogenesis, general concepts can emerge that may apply to other settings, including tumor angiogenesis. One concept that has emerged is that despite participation of multiple stimulatory factors for ocular neovascularization, VEGF plays an essential role and interruption of VEGF signaling is an important therapeutic strategy. Another concept is that while most studies have focused on prevention of ocular neovascularization, regression of new vessels is desirable and is achievable with at least three agents, **combretastatin A-4** phosphate, pigment epithelium-derived factor, and angiopoietin-2. Finally, endostatin and angiostatin, which have been sources of controversy because of inconsistent results in tumor models, have been shown to have good efficacy when delivered by gene transfer in models of ocular neovascularization. These results provide leads for new ocular treatments and perspective for evaluation of studies of neovascularization in extraocular tissues.

CONTROLLED TERM: Check Tags: Human; Support, Non-U.S. Gov't; Support, U.S. Gov't, P.H.S.
Angiogenesis Inhibitors: TU, therapeutic use
Animals
Choroid: BS, blood supply
Disease Models, Animal
Endothelial Growth Factors: PH, physiology
Enzyme Inhibitors: TU, therapeutic use
*Eye: BS, blood supply
Intercellular Signaling Peptides and Proteins: PH, physiology
Lymphokines: PH, physiology
Mice
Models, Biological
Neovascularization, Pathologic: DT, drug therapy

*Neovascularization, Pathologic: GE, genetics
*Neovascularization, Pathologic: PA, pathology
Nitric-Oxide Synthase: AI, antagonists & inhibitors
*Retinal Vessels: PA, pathology
Vascular Endothelial Growth Factor A
Vascular Endothelial Growth Factors

CHEMICAL NAME: 0 (Angiogenesis Inhibitors); 0 (Endothelial Growth Factors); 0 (Enzyme Inhibitors); 0 (Intercellular Signaling Peptides and Proteins); 0 (Lymphokines); 0 (Vascular Endothelial Growth Factor A); 0 (Vascular Endothelial Growth Factors); EC 1.14.13.39 (Nitric-Oxide Synthase)

L89 ANSWER 4 OF 27 DRUGU COPYRIGHT 2004 THOMSON DERWENT on STN DUPLICATE 6
ACCESSION NUMBER: 2002-24213 DRUGU P
TITLE: Importance of tumor size and nitric oxide levels in determining tumor sensitivity to **combretastatin A-4** disodium phosphate.
AUTHOR: Murata R; Horsman M R
LOCATION: Aarhus, Den.
SOURCE: Proc.Am.Assoc.Cancer Res. (43, 93 Meet., 157, 2002) ISSN: 0197-016X
AVAIL. OF DOC.: Danish Cancer Society, Dept. Experimental Clinical Oncology, Aarhus, Denmark.
LANGUAGE: English
DOCUMENT TYPE: Journal

ABSTRACT:

Although the novel vascular targeting drug i.p. **combretastatin** ***A*** **-4** disodium phosphate (CA4DP) induces vascular damage in a wide spectrum of tumor models the degree of activity can be highly variable. The aim of this study was to investigate some of the important factors that may determine this activity in 2 murine tumor models. C3H mammary carcinoma showed no size dependent response to CA4DP and was generally less response to the vascular damaging agent than the KHT sarcoma that did show a tumor size dependency. Interestingly, the response of both tumor types could be substantially improved by **inhibiting nitric oxide** production by co-administration of 1.v. nitro-L-arginine (NLA). (conference abstract: 93rd Annual Meeting of the American Association for Cancer Research, San Francisco, California, USA, 2002).

SECTION HEADING: P Pharmacology

CLASSIF. CODE: 52 Chemotherapy - non-clinical
66 Drug Interactions

CONTROLLED TERM:
C3H *OC; MAMMA *OC; MAMMA-DISEASE *OC; CARCINOMA *OC; KHT *OC; SARCOMA *OC; ANIMAL-NEOPLASM *OC; MOUSE *FT; IN-VIVO *FT; ATHYMIC *FT; NUDE *FT; COMB. *FT; NITRIC-OXIDE *FT; LAB.ANIMAL *FT
[01] **COMBRETASTATIN-A-4** *PH; **COMBRETASTATIN-A-4** *DI; PHOSPHATE *DI; PHOSPHATE *PH; NITROARGININE-N-G *DI; SODIUM *PH; SODIUM *DI; COMBRESA4 *RN; SODIUM-SALT *FT; CYTOSTATIC *FT; ANGIOGENESIS-INHIBITOR *FT; I.P. *FT; ALONE *FT; INJECTION *FT; CYTOSTATICS *FT; ANGIOGENESIS-INHIBITORS *FT; PH *FT; DI *FT

CAS REGISTRY NO.: **117048-59-6**
[02] NITROARGININE-N-G *PH; NITROARGININE-N-G *DI; **COMBRETASTATIN-A-4** *DI; NOARG-N-G

*RN; SYNERGIST *FT; **NITRIC-OXIDE**
-SYNTHASE-**INHIBITOR** *FT; I.V. *FT; INJECTION *FT;
NITRIC-OXIDE-SYNTHASE-**INHIBITORS**
*FT; PH *FT; DI *FT
CAS REGISTRY NO.: **2149-70-4**
FIELD AVAIL.: AB; LA; CT
FILE SEGMENT: Literature

L89 ANSWER 5 OF 27 DRUGU COPYRIGHT 2004 THOMSON DERWENT on STN DUPLICATE 9
ACCESSION NUMBER: 2000-38636 DRUGU P
TITLE: Determinants of anti-vascular action by **combretastatin A.4** phosphate: role of nitric oxide.
AUTHOR: Parkins C S; Holder A L; Hill S A; Chaplin D J; Tozer G M
CORPORATE SOURCE: Aventis
LOCATION: Northwood, U.K.; Vitry- Alfortville; Vitry sur Seine, Fr.
SOURCE: Br.J.Cancer (83, No. 6, 811-16, 2000) 4 Fig. 33 Ref.
CODEN: BJCAAI ISSN: 0007-0920
AVAIL. OF DOC.: Tumour Microcirculation Group, Gray Laboratory Cancer Research Trust, Mount Vernon Hospital, Northwood, Middlesex, HA6 2JR, England.
LANGUAGE: English
DOCUMENT TYPE: Journal

ABSTRACT:

The antivascular action of i.p. **combretastatin A-4** -phosphate Na2 (CA-4-P, Oxigene) was determined in mice bearing breast CaNT adenocarcinoma and round cell SaS sarcoma cells. Simultaneous administration of CA-4-P with nitroarginine-N-G (Sigma-Chem.) resulted in enhanced vascular damage and cytotoxicity in both tumor types. NO was shown to modify the tumor vascular damage induced by CA-4-P. This appeared to be due to tumor-dependent levels of NO acting to reduce the tumor infiltration of neutrophils, thereby reducing the damage to the tumor vascular endothelium after CA-4-P. The understanding of the role of NO in tumor vascular infiltration is important both for the development of CA-4-P as a cancer chemotherapeutic agent and for the future development of new vascular targeting agents.

SECTION HEADING: P Pharmacology

CLASSIF. CODE: 52 Chemotherapy - non-clinical
66 Drug Interactions

CONTROLLED TERM:
SARCOMA *OC; ADENOCARCINOMA *OC; MAMMA *OC; MAMMA-DISEASE *OC; ANIMAL-NEOPLASM *OC; MOUSE *FT; IN-VIVO *FT; I.P. *FT; CYTOSTATIC *FT; NEUTROPHIL *FT; NITRIC-OXIDE *FT; FREE-RADICAL *FT; VESSEL *FT; FUNCTION *FT; COMB. *FT; LAB.ANIMAL *FT; INJECTION *FT; LEUKOCYTE *FT
[01] **COMBRETASTATIN-A-4** *PH; **COMBRETASTATIN-A-4** *DI; PHOSPHATE *PH; NITROARGININE-N-G *DI; COMBRESA4 *RN; OXIGENE *FT; MODE-OF-ACT. *FT; CYTOSTATICS *FT; ANGIOGENESIS-INHIBITORS *FT; PH *FT; DI *FT
CAS REGISTRY NO.: **117048-59-6**
[02] NITROARGININE-N-G *PH; NITROARGININE-N-G *DI; SIGMA-CHEM. *FT; **COMBRETASTATIN-A-4** *DI; NOARG-N-G *RN; **NITRIC-OXIDE**-SYNTHASE-**INHIBITOR** *FT; **NITRIC-OXIDE**-SYNTHASE-**INHIBITORS** *FT; PH *FT; DI *FT
CAS REGISTRY NO.: **2149-70-4**
FIELD AVAIL.: AB; LA; CT

FILE SEGMENT: Literature

L89 ANSWER 6 OF 27 DRUGU COPYRIGHT 2004 THOMSON DERWENT on STN
ACCESSION NUMBER: 2002-11176 DRUGU P G
TITLE: Enhancement of **combretastatin A4** phosphate activity by **nitric oxide** synthase **inhibitors** of different structural classes.
AUTHOR: Davis P D; Thomson P; Naylor M A; Nolan J; Lewis G S; Hill S A
CORPORATE SOURCE: Angiogene; Gray-Lab.Cancer-Res.Trust
LOCATION: Aston Rowant; Northwood, U.K.
SOURCE: Clin.Cancer Res. (7, Suppl., 3656S, 2001)
CODEN: CCREF ISSN: 1078-0432
AVAIL. OF DOC.: Angiogene Pharmaceuticals Ltd, Aston Rowant, England.
LANGUAGE: English
DOCUMENT TYPE: Journal

ABSTRACT:

Combretastatin A4 phosphate (CA4P) reduced vascular volume in mice bearing CaNT tumors. The NOS inhibitors L-nitroarginine (L-NNA), AMT and AMP enhanced the vascular volume reduction by CA4P. The induction of tumor necrosis by CA4P was also enhanced both in CaNT and SaS tumors. ANG-500, designed to give provide both combrestatin A4 and L-NNA by cleavage after in vivo administration, was more potent than CA4P against the CaNT tumor in reduction of vascular volume, induction of necrosis and reduction in surviving fraction per gram. Growth delay was achieved with a single dose of ANG-500. The vascular targeting activity of CA4P can be enhanced by NOS inhibitors of different structural classes. (conference abstract: AACR-NCI-EORTC International Conference on Molecular Targets and Cancer Therapeutics, Miami Beach, Florida, USA, 2001).

SECTION HEADING: P Pharmacology
G Galenics

CLASSIF. CODE: 29 Pharmaceutics
52 Chemotherapy - non-clinical
65 Drug Delivery
66 Drug Interactions
72 New Drugs
73 Trial Preparations

CONTROLLED TERM:
ANIMAL-NEOPLASM *OC; IN-VIVO *FT; MOUSE *FT; NECROSIS *FT; VESSEL *FT; BIOPHARM. *FT; LAB.ANIMAL *FT
[01] **COMBRETASTATIN-A-4** *PH; **COMBRETASTATIN-A-4** *DI; NITROARGININE-N-G *DI; COMBRESA4 *RN; CYTOSTATIC *FT; ANGIOGENESIS-INHIBITOR *FT; COMB. *FT; ALONE *FT; CYTOSTATICS *FT; ANGIOGENESIS-INHIBITORS *FT; PH *FT; DI *FT
CAS REGISTRY NO.: **117048-59-6**
[02] NITROARGININE-N-G *PH; NITROARGININE-N-G *DI; **COMBRETASTATIN-A-4** *DI; NOARG-N-G *RN; **NITRIC-OXIDE**-SYNTHASE-**INHIBITOR** *FT; SYNERGIST *FT; COMB. *FT; ALONE *FT; **NITRIC-OXIDE**-SYNTHASE-**INHIBITORS** *FT; PH *FT; DI *FT
CAS REGISTRY NO.: **2149-70-4**
[03] ANG-500 *PH; DR0059221 *RN; PRODRUG *FT; ANGIOGENESIS-INHIBITOR *FT; CYTOSTATIC *FT; **NITRIC-OXIDE**-SYNTHASE-**INHIBITOR** *FT; SINGLE *FT; DOSAGE *FT;

NEW *FT; TRIAL-PREP. *FT; **NITRIC-OXIDE**
-SYNTHASE-**INHIBITORS** *FT; CYTOSTATICS *FT;
ANGIOGENESIS-INHIBITORS *FT; BIOPHARM. *FT; PH *FT
FIELD AVAIL.: AB; LA; CT
FILE SEGMENT: Literature

L89 ANSWER 7 OF 27 DRUGU COPYRIGHT 2004 THOMSON DERWENT on STN
ACCESSION NUMBER: 2002-04124 DRUGU P
TITLE: Tumor nitric oxide levels and vascular targeting with **combretastatin A-4**-P.
AUTHOR: Tozer G M; Prise V E; Wilson I
CORPORATE SOURCE: Gray-Lab.Cancer-Res.
LOCATION: Northwood, U.K.
SOURCE: Proc.Am.Assoc.Cancer Res. (42, 92 Meet., 824, 2001) ISSN: 0197-016X
AVAIL. OF DOC.: Gray Laboratory Cancer Research Trust, Middlesex, England.
LANGUAGE: English
DOCUMENT TYPE: Journal

ABSTRACT:

I.p. **combretastatin A4**-P (CA-4-P) reduced tumor blood flow in rats bearing subcutaneous P22 tumors. L-NNA and its pro-drug L-NAME, selectively reduced tumor blood flow. Combined chronic p.o. and i.p. L-NAME and CA-4-P produced a more than additive effect in the tumor. Acute inhibition of NOS at the time of CA-4-P administration had no more than an additive effect. Constitutively produced nitric oxide synthase (NOS), rather than inducible NOS (iNOS) has an important role in the maintenance of blood flow in the P22 tumor. A vascular effect of chronic NOS inhibition, rather than acute tumor blood flow reduction at the time of CA-4-P administration, sensitizes the tumor vasculature to the damaging effects of CA-4-P. This combination may be therapeutically useful. (conference abstract: 92nd Annual Meeting of the American Association for Cancer Research, New Orleans, Louisiana, USA, 2001).

SECTION HEADING: P Pharmacology

CLASSIF. CODE: 8 Pharmacokinetics
52 Chemotherapy - non-clinical
66 Drug Interactions

CONTROLLED TERM:
P22 *OC; ANIMAL-NEOPLASM *OC; IN-VIVO *FT; I.P. *FT; RAT *FT;
BLOOD-FLOW *FT; ALONE *FT; COMB. *FT; EC-1.14.13.39 *FT;
INJECTION *FT; LAB.ANIMAL *FT; HEMODYNAMICS *FT;
NITRIC-OXIDE-SYNTHASE *FT
[01] **COMBRETASTATIN-A-4** *PH;
COMBRETASTATIN-A-4 *DM;
NITROARGININE-N-G-METHYLESTER *DI; NITROARGININE-N-G *DI;
COMBRESA4 *RN; CYTOSTATIC *FT; CYTOSTATICS *FT;
ANGIOGENESIS-INHIBITORS *FT; PH *FT; DM *FT
CAS REGISTRY NO.: **117048-59-6**
[02] NITROARGININE-N-G-METHYLESTER *PH; NITROARGININE-N-G-METHYLESTER *DM; NITROARGININE-N-G-METHYLESTER *DI; **COMBRETASTATIN-A-4** *DI; NO2ARGMEE *RN; PRODRUG *FT; BIOSYNTH. *FT; P.O. *FT; **NITRIC-OXIDE**-SYNTHASE-**INHIBITOR** *FT; ACUTE *FT; CHRON. *FT; DOSAGE *FT; BIOPHARM. *FT; VASOCONSTRICTORS *FT; **NITRIC-OXIDE**-SYNTHASE-**INHIBITORS** *FT; PH *FT; DM *FT; DI *FT
[03] NITROARGININE-N-G *PH; NITROARGININE-N-G *DM; NITROARGININE-N-G *DI; **COMBRETASTATIN-A-4** *DI; NOARG-N-G *RN; PRODRUG *FT; **NITRIC-**

OXIDE-SYNTHASE-**INHIBITOR** *FT; BIOPHARM.
*FT; **NITRIC-OXIDE**-SYNTHASE-
INHIBITORS *FT; PH *FT; DM *FT; DI *FT
CAS REGISTRY NO.: **2149-70-4**
FIELD AVAIL.: AB; LA; CT
FILE SEGMENT: Literature

L89 ANSWER 8 OF 27 CAPLUS COPYRIGHT 2004 ACS on STN DUPLICATE 8
ACCESSION NUMBER: 2000:592549 CAPLUS
DOCUMENT NUMBER: 133:172166
TITLE: Combinations for the treatment of diseases involving angiogenesis
INVENTOR(S): Davis, Peter David
PATENT ASSIGNEE(S): Angiogene Pharmaceuticals Ltd., UK
SOURCE: PCT Int. Appl., 18 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000048591	A1	20000824	WO 2000-GB511	20000215
W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
BR 2000008254	A	20011106	BR 2000-8254	20000215
EP 1161235	A1	20011212	EP 2000-903832	20000215
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
JP 2002537251	T2	20021105	JP 2000-599383	20000215
NZ 513429	A	20031031	NZ 2000-513429	20000215
ZA 2001006688	A	20020814	ZA 2001-6688	20010814
NO 2001003966	A	20011015	NO 2001-3966	20010815

PRIORITY APPLN. INFO.: GB 1999-3404 A 19990216
WO 2000-GB511 W 20000215

ED Entered STN: 25 Aug 2000
AB Compns. for the inhibition of the formation of new vasculature by angiogenesis are provided comprising the combination of a vasculature damaging agent and an inhibitor of the formation or action of nitric oxide in mammalian systems. An example is given showing enhancement of combretastatin A4 phosphate activity in SaS tumors by coadministration of L-NG-nitroarginine.
IT **695-34-1**, 2-Amino-4-methylpyridine **2149-70-4**, L-NG-Nitroarginine **17035-90-4 222030-63-9**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(combinations for the treatment of diseases involving angiogenesis)
IT **36889-13-1 53774-63-3 57444-72-1 156719-37-8**, L-Thiocitrulline **156719-38-9**, L-Homothiocitrulline **156719-41-4**, S-Methyl-L-thiocitrulline

RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(combinations for the treatment of diseases involving angiogenesis)
IT **10102-43-9**, **Nitric oxide**, biological studies
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(**inhibitors**; combinations for the treatment of diseases involving angiogenesis)
REFERENCE COUNT: 8 THERE ARE 8 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L89 ANSWER 9 OF 27 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2002:142717 CAPLUS
DOCUMENT NUMBER: 136:183937
TITLE: Preparation and use of cis-stilbene derivatives with vascular damaging activity
INVENTOR(S): Davis, Peter David
PATENT ASSIGNEE(S): Angiogene Pharmaceuticals Ltd., UK
SOURCE: PCT Int. Appl., 21 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002014329	A1	20020221	WO 2001-GB3668	20010815
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
AU 2001077629	A5	20020225	AU 2001-77629	20010815
EP 1311514	A1	20030521	EP 2001-955467	20010815
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				
US 2003181424	A1	20030925	US 2003-367606	20030214

PRIORITY APPLN. INFO.: GB 2000-19944 A 20000815
WO 2001-GB3668 W 20010815
OTHER SOURCE(S): MARPAT 136:183937
ED Entered STN: 22 Feb 2002
AB The invention describes the prepn. of compns. which contain salts comprising, as an acidic component, compd. [I, wherein: R1, R2 and R3, independently = alkyl; R4 = alkoxy, haloalkoxy, alkyl, haloalkyl, alkenyl, alkynyl, alkylthio, alkylsulphinyl, alkylsulfonyl, hydroxy, halo; R5 = H, alkoxy, alkyl, alkylthio, hydroxy, phosphate or halo]; and, as the basic component, a compd. selected from the group consisting of compd. [II, wherein: R6 = H, alkyl; R7 = alkyl, alkylamino, dialkylamino, nitroamino, hydrazine, mercapto, alkylthio; X = CH2, CH2CH2, CH2S, CH2CH2S; Y = NH, S], or compd. [III, wherein: R8 = alkyl, aminoalkyl; R9 = H, alkyl, or optionally substituted Ph], or compd. [IV, wherein: Z = O, S, CH2, CHR13, or a bond; R10, R11, R12 and R13, independently = H, alkyl], or compd. [V, wherein: R14 = alkyl], and the pharmaceutically acceptable solvates and hydrates thereof. Thus, a mixt. of combretastatin A4 phosphate and L-NG-nitroarginine Me ester was dissolved in water, stirred for 18 h, and freeze-dried to produce (Z)-2-methoxy-5-[2-(3,4,5-trimethoxyphenyl)ethenyl]phenyl di(1-methoxycarbonyl-4-N'-nitroguanidinobutylammonium) phosphate. The prepd. compns. are useful as antitumor agents, and are angiogenesis inhibitors displaying vascular

damaging activity. Biol. data are given.

IT **222030-63-9**
RL: PAC (Pharmacological activity); RCT (Reactant); THU (Therapeutic use); BIOL (Biological study); RACT (Reactant or reagent); USES (Uses)
(prepn. and use of cis-stilbene derivs. with vascular damaging activity)

IT **2149-70-4**
RL: RCT (Reactant); RACT (Reactant or reagent)
(prepn. and use of cis-stilbene derivs. with vascular damaging activity)

REFERENCE COUNT: 7 THERE ARE 7 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L89 ANSWER 10 OF 27 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2000:592548 CAPLUS
DOCUMENT NUMBER: 133:177486
TITLE: Preparation of substituted stilbene compounds with vascular damaging activity
INVENTOR(S): Davis, Peter David
PATENT ASSIGNEE(S): Angiogene Pharmaceuticals Ltd., UK
SOURCE: PCT Int. Appl., 31 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000048590	A1	20000824	WO 2000-GB503	20000215
W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
EP 1154767	A1	20011121	EP 2000-903824	20000215
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
JP 2002537250	T2	20021105	JP 2000-599382	20000215

PRIORITY APPLN. INFO.: GB 1999-3403 A 19990216
WO 2000-GB503 W 20000215

OTHER SOURCE(S): MARPAT 133:177486
ED Entered STN: 25 Aug 2000
AB A vascular damaging agent AXB (A = substituted cis-stilbene; X = linker bond, atom, or group; B = moiety derived from an inhibitor of the formation or action of NO in mammalian systems), is claimed. Thus, (Z)-1-[3-(N-.alpha.-tert-butoxycarbonyl-N-.omega.-nitroarginyloxy)-4-methoxyphenyl]-2-(3,4,5-trimethoxyphenyl)ethene was stirred with CF3CO2H in CH2Cl2 to give (Z)-1-(4-methoxy-3-NG-nitroarginyloxyphenyl)-2-(3,4,5-trimethoxyphenyl)ethene. The latter at 50 mg/kg i.p. in mice bearing CaNT or SaS tumors gave 95% redn. in vascular vol. and 91-100% tumor necrosis.

IT **125978-95-2**, **Nitric oxide** synthase
RL: BSU (Biological study, unclassified); MSC (Miscellaneous); BIOL (Biological study)
(**inhibitors**; prepn. of substituted stilbene compds. with vascular damaging activity)

IT **117048-59-6**
RL: RCT (Reactant); RACT (Reactant or reagent)

(prepn. of substituted stilbene compds. with vascular damaging activity)
REFERENCE COUNT: 5 THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L89 ANSWER 11 OF 27 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1984:622096 CAPLUS
DOCUMENT NUMBER: 101:222096
TITLE: Functional group contributions to drug-receptor interactions
AUTHOR(S): Andrews, P. R.; Craik, D. J.; Martin, J. L.
CORPORATE SOURCE: Victorian Coll. Pharm. Ltd., Parkville, 3052, Australia
SOURCE: Journal of Medicinal Chemistry (1984), 27(12), 1648-57
CODEN: JMCMAR; ISSN: 0022-2623
DOCUMENT TYPE: Journal
LANGUAGE: English
ED Entered STN: 22 Dec 1984
AB To overcome the difficulties in estg. the potential bond strengths involved in the interaction between a drug and a reasonable matched receptor, 200 drugs and enzyme inhibitors chosen on the basis of their apparent tight binding to their corresponding receptor sites, were used to provide a statistical est. of the strength of noncovalent bonds assocd. with each functional groups in an av. drug-receptor environment. Values are presented to det. the goodness of fit of a drug to its receptor by comparing the obsd. binding const. to the av. binding energy calcd. by summing the intrinsic binding energies of the component groups and then subtracting 2 entropy related terms. Drugs such as diazepam [439-14-5] that match their receptors well have a measured binding energy exceeding the calcd. av. value, whereas others such as buprenorphine [52485-79-7] who match their receptor less than the av. have binding energies less the calcd. av. value. In addn. the binding energies of 3 central nervous system active drugs and representative amino acids within a polypeptide mol. are also given. General principles for the application of intrinsic binding energies in drug design and structure-activity relations are discussed.
IT **56-87-1**, biological studies **38838-26-5**
RL: PROC (Process)
(binding of, with receptors)

L89 ANSWER 12 OF 27 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
DUPLICATE 2
ACCESSION NUMBER: 2003:153852 BIOSIS
DOCUMENT NUMBER: PREV200300153852
TITLE: The First International Conference on Vascular Targeting: Meeting overview.
AUTHOR(S): Thorpe, Philip E. [Reprint Author]; Chaplin, David J.; Blakey, David C.
CORPORATE SOURCE: Department of Pharmacology, University of Texas Southwestern Medical Center, Dallas, TX, 75390, USA
philip.thorpe@utsouthwestern.edu
SOURCE: Cancer Research, (March 1 2003) Vol. 63, No. 5, pp. 1144-1147. print.
ISSN: 0008-5472 (ISSN print).
DOCUMENT TYPE: Article
Conference; Report; (Meeting Report)
LANGUAGE: English
ENTRY DATE: Entered STN: 26 Mar 2003
Last Updated on STN: 26 Mar 2003

ABSTRACT:The First International Conference on Vascular Targeting focused on vascular targeting agents (VTAs) that occlude or destroy the pre-existing blood vessels of solid tumors. The VTAs cause a rapid shutdown in the blood supply to the tumor that kills tumor cells by depriving them of oxygen and nutrients. The VTAs are distinct from antiangiogenic agents, which prevent new blood vessel formation. Two major types of VTAs are being developed for cancer: the ligand-directed VTAs that use antibodies, peptides, and growth factors to deliver toxins, procoagulants, and proapoptotic effectors to tumor endothelium, and the small molecule VTAs that do not specifically localize to tumor endothelium but exploit pathophysiological differences between tumor and normal tissue endothelia to induce acute vascular shutdown in tumors. Both approaches were described at the meeting and highlighted the variety of VTAs in preclinical development, their selectivity for tumor endothelium, their rapid antitumor effects, and the improved activity seen when combined with other anticancer approaches (antiproliferative chemotherapeutic drugs, radiation, radiolabeled antibodies, **nitric oxide** synthetase ***inhibitors*** , and anti-angiogenic agents). Early clinical studies were summarized for the small molecule VTAs: the antitubulin drugs, ***combretastatin*** **A4** phosphate (CA4P) and ZD6126, and the flavonoid, 5,6-dimethylxanthenone-4-acetic acid (DMXAA). The agents lacked the bone marrow and gastrointestinal toxicities associated with antiproliferative chemotherapy. As a marker of biological effect, blood flow reductions in tumors were measured using magnetic resonance imaging or positron emission tomography for all of the agents tested, and single-agent clinical activity was seen. These agents are now being evaluated in combined modality studies to see whether the impressive results obtained in experimental models can be translated into humans.

CONCEPT CODE:
Biochemistry studies - General 10060
Pathology - Therapy 12512
Digestive system - Pathology 14006
Cardiovascular system - Physiology and biochemistry 14504
Blood - Blood, lymphatic and reticuloendothelial pathologies 15006
Pharmacology - General 22002
Pharmacology - Clinical pharmacology 22005
Pharmacology - Cardiovascular system 22010
Toxicology - General and methods 22501
Toxicology - Pharmacology 22504
Neoplasms - Pathology, clinical aspects and systemic effects 24004
Neoplasms - Therapeutic agents and therapy 24008
Neoplasms - Blood and reticuloendothelial neoplasms 24010

INDEX TERMS: Major Concepts
Cardiovascular System (Transport and Circulation); Pharmacology; Tumor Biology

INDEX TERMS: Parts, Structures, & Systems of Organisms
blood vessels: circulatory system, formation; endothelium

INDEX TERMS: Diseases
bone marrow toxicity: blood and lymphatic disease, toxicity, drug-induced

INDEX TERMS: Diseases
cancer: neoplastic disease, drug therapy
Neoplasms (MeSH)

INDEX TERMS: Diseases
gastrointestinal toxicity: digestive system disease, toxicity, drug-induced

INDEX TERMS: Diseases
nonmalignant disease: disease-miscellaneous

INDEX TERMS: Chemicals & Biochemicals
5,6-dimethylxanthenone-4-acetic acid [DMXAA]: antineoplastic-drug, cardiovascular-drug, clinical

Searched by Barb O'Bryen, STIC 571-272-2518

trial; ZD6126: antineoplastic-drug, cardiovascular-drug, clinical trial; antiangiogenic agents: cardiovascular-drug; antiproliferative chemotherapeutic drugs: antineoplastic-drug; **combretastatin A4** phosphate: antineoplastic-drug, cardiovascular-drug, clinical trial; flavonoids: antineoplastic-drug, cardiovascular-drug; **nitric oxide** synthase **inhibitors**: enzyme inhibitor-drug; radiolabled antibodies; tubulin-binding agents: antineoplastic-drug, cardiovascular-drug; vascular targeting agents: antineoplastic-drug, cardiovascular-drug

INDEX TERMS: Methods & Equipment
magnetic resonance imaging: clinical techniques, diagnostic techniques, imaging and microscopy techniques, laboratory techniques; positron emission tomography: clinical techniques, diagnostic techniques, imaging and microscopy techniques, laboratory techniques; radiation therapy: clinical techniques, therapeutic and prophylactic techniques

INDEX TERMS: Miscellaneous Descriptors
blood flow reduction; vascular targeting

ORGANISM: Classifier
Hominidae 86215
Super Taxa
Primates; Mammalia; Vertebrata; Chordata; Animalia
Organism Name
human (common): patient
Taxa Notes
Animals, Chordates, Humans, Mammals, Primates, Vertebrates

ORGANISM: Classifier
Muridae 86375
Super Taxa
Rodentia; Mammalia; Vertebrata; Chordata; Animalia
Organism Name
mouse (common): animal model
Taxa Notes
Animals, Chordates, Mammals, Nonhuman Vertebrates, Nonhuman Mammals, Rodents, Vertebrates

REGISTRY NUMBER: 117570-53-3 (5,6-dimethylxanthenone-4-acetic acid)
117570-53-3 (DMXAA)
219923-05-4 (ZD6126)
222030-63-9 (**combretastatin A4** phosphate)

L89 ANSWER 13 OF 27 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
DUPLICATE 10

ACCESSION NUMBER: 1999:225372 BIOSIS
DOCUMENT NUMBER: PREV199900225372
TITLE: **Combretastatin A-4** phosphate as a tumor vascular-targeting agent: Early effects in tumors and normal tissues.
AUTHOR(S): Tozer, Gillian M. [Reprint author]; Prise, Vivien E.; Wilson, John; Locke, Rosalind J.; Vojnovic, Borivoj; Stratford, Michael R. L.; Dennis, Madeleine F.; Chaplin, David J.
CORPORATE SOURCE: Tumor Microcirculation Group, Gray Laboratory Cancer Research Trust, Mount Vernon Hospital, Northwood, Middlesex, HA6 2JR, UK
SOURCE: Cancer Research, (April 1, 1999) Vol. 59, No. 7, pp. 1626-1634. print.

CODEN: CNREA8. ISSN: 0008-5472.
DOCUMENT TYPE: Article
LANGUAGE: English
ENTRY DATE: Entered STN: 7 Jun 1999
Last Updated on STN: 7 Jun 1999

ABSTRACT:The potential for tumor vascular-targeting by using the tubulin destabilizing agent disodium **combretastatin A-4** 3-0-phosphate (CA-4-P) was assessed in a rat system. This approach aims to shut down the established tumor vasculature, leading to the development of extensive tumor cell necrosis. The early vascular effects of CA-4-P were assessed in the s.c. implanted P22 carcinosarcoma and in a range of normal tissues. Blood flow was measured by the uptake of radiolabeled iodoantipyrine, and quantitative autoradiography was used to measure spatial heterogeneity of blood flow in tumor sections. CA-4-P (100 mg/kg i.p.) caused a significant increase in mean arterial blood pressure at 1 and 6 h after treatment and a very large decrease in tumor blood flow, which-by 6 h-was reduced approximately 100-fold. The spleen was the most affected normal tissue with a 7-fold reduction in blood flow at 6 h. Calculations of vascular resistance revealed some vascular changes in the heart and kidney for which there were no significant changes in blood flow. Quantitative autoradiography showed that CA-4-P increased the spatial heterogeneity in tumor blood flow. The drug affected peripheral tumor regions less than central regions. Administration of CA-4-P (30 mg/kg) in the presence of the **nitric oxide** synthase **inhibitor**, Nomega-nitro-L-arginine methyl ester, potentiated the effect of CA-4-P in tumor tissue. The combination increased tumor vascular resistance 300-fold compared with less than 7-fold for any of the normal tissues. This shows that tissue production of nitric oxide protects against the damaging vascular effects of CA-4-P. Significant changes in tumor vascular resistance could also be obtained in isolated tumor perfusions using a cell-free perfusate, although the changes were much less than those observed in vivo. This shows that the action of CA-4-P includes mechanisms other than those involving red cell viscosity, intravascular coagulation, and neutrophil adhesion. The uptake of CA-4-P and **combretastatin A-**
4 (CA-4) was more efficient in tumor than in skeletal muscle tissue and dephosphorylation of CA-4-P to CA-4 was faster in the former. These results are promising for the use of CA-4-P as a tumor vascular-targeting agent.

CONCEPT CODE: Neoplasms - General 24002
Cytology - Animal 02506
Biochemistry studies - General 10060
Metabolism - General metabolism and metabolic pathways 13002
Cardiovascular system - General and methods 14501
Blood - General and methods 15001
Urinary system - General and methods 15501
Muscle - General and methods 17501
General biology - Miscellaneous 00532
INDEX TERMS: Major Concepts
Biochemistry and Molecular Biophysics; Tumor Biology
INDEX TERMS: Parts, Structures, & Systems of Organisms
heart: circulatory system; kidney: excretory system; skeletal muscle: muscular system; spleen: blood and lymphatics, immune system
INDEX TERMS: Chemicals & Biochemicals
combretastatin A-4
phosphate: dephosphorylation, tumor vascular-targeting agent, uptake; nitric oxide: production
INDEX TERMS: Miscellaneous Descriptors
mean arterial blood pressure; tumor blood flow; vascular resistance
ORGANISM: Classifier
Cricetidae 86310
Super Taxa

Rodentia; Mammalia; Vertebrata; Chordata; Animalia
Organism Name
P22 cell line: rat carcinosarcoma cell
Taxa Notes
Animals, Chordates, Mammals, Nonhuman Vertebrates, Nonhuman Mammals, Rodents, Vertebrates
ORGANISM: Classifier
Muridae 86375
Super Taxa
Rodentia; Mammalia; Vertebrata; Chordata; Animalia
Organism Name
rat: animal model
Taxa Notes
Animals, Chordates, Mammals, Nonhuman Vertebrates, Nonhuman Mammals, Rodents, Vertebrates
REGISTRY NUMBER: 10102-43-9 (nitric oxide)
14265-44-2 (PHOSPHATE)
82855-09-2 (COMBRETASTATIN)

L89 ANSWER 14 OF 27 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED.
on STN DUPLICATE 1
ACCESSION NUMBER: 2003453009 EMBASE
TITLE: Ocular neovascularization: A valuable model system.
AUTHOR: Campochiaro P.A.; Hackett S.F.
CORPORATE SOURCE: P.A. Campochiaro, Depts. of Ophthalmol. and Neurosci., Johns Hopkins Univ. Sch. of Medicine, Maumenee 719, 600 N. Wolfe Street, Baltimore, MD 21287-9277, United States. pcampo@inmi.edu
SOURCE: Oncogene, (2 Oct 2003) 22/43 (6537-6548).
Refs: 133
ISSN: 0950-9232 CODEN: ONCNES
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 005 General Pathology and Pathological Anatomy
012 Ophthalmology
016 Cancer
030 Pharmacology
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English
ABSTRACT:
There is no unique formula for angiogenesis. Instead there is a large group of potential participating proteins that interact in complex ways. Depending upon the surrounding cell types and the relative expression levels of angiogenesis-related proteins, the 'angiogenesis cascade' can vary. Therefore, it is valuable to study and compare the role of proteins in several well-characterized vascular beds. The eye provides a useful model system, because it contains several vascular beds sandwiched between avascular tissue. This allows for unequivocal identification and quantitation of new vessels. Retina-specific promoters combined with inducible promoter systems provide a means to regulate the expression of proteins of interest. As a relatively isolated compartment, the eye also provides advantages for gene transfer. By gaining insight regarding the molecular signals involved in various types of ocular angiogenesis, general concepts can emerge that may apply to other settings, including tumor angiogenesis. One concept that has emerged is that despite participation of multiple stimulatory factors for ocular neovascularization, VEGF plays an essential role and interruption of VEGF signaling is an important therapeutic strategy. Another concept is that while most studies have focused on prevention of ocular neovascularization, regression of new vessels is desirable and is achievable with at least three agents, combretastatin A-4 phosphate, pigment epithelium-derived factor, and angiopoietin-2. Finally, endostatin and angiostatin, which have been sources of

controversy because of inconsistent results in tumor models, have been shown to have good efficacy when delivered by gene transfer in models of ocular neovascularization. These results provide leads for new ocular treatments and perspective for evaluation of studies of neovascularization in extraocular tissues.

CONTROLLED TERM: Medical Descriptors:
*retina macula age related degeneration: ET, etiology
*retina neovascularization: DT, drug therapy
*retina neovascularization: ET, etiology
*subretinal neovascularization: DT, drug therapy
*subretinal neovascularization: ET, etiology
retinopathy: ET, etiology
retina macula degeneration: ET, etiology
neovascularization (pathology): DT, drug therapy
neovascularization (pathology): ET, etiology
signal transduction
transgenic mouse
colorectal cancer: ET, etiology
colorectal cancer: PC, prevention
thyroid cancer: DT, drug therapy
cancer: DT, drug therapy
cancer: ET, etiology
cancer: PC, prevention
angiogenesis
enzyme inhibition
gene transfer
isotope labeling
human
nonhuman
mouse
clinical article
clinical trial
animal model
review
priority journal
Drug Descriptors:
*vasculotropin
*pigment epithelium derived factor
***combretastatin A4: CT, clinical trial**
***combretastatin A4: AD, drug administration**
***combretastatin A4: DO, drug dose**
***combretastatin A4: DT, drug therapy**
***combretastatin A4: PD, pharmacology**
***combretastatin A4: IP, intraperitoneal drug administration**
*vasculotropin antibody: CT, clinical trial
*vasculotropin antibody: AD, drug administration
*vasculotropin antibody: DT, drug therapy
*vasculotropin antibody: PK, pharmacokinetics
*vasculotropin antibody: VI, intravitreal drug administration
*nepafenac: AD, drug administration
*nepafenac: PK, pharmacokinetics
*nepafenac: PD, pharmacology
*nepafenac: TP, topical drug administration
vasculotropin receptor
rhodopsin
receptor subtype
complementary DNA
messenger RNA
growth hormone

somatomedin C
fibroblast growth factor 2: EC, endogenous compound
angiopoietin 1
angiopoietin 2
iodine 125
immunoglobulin F(ab')2 fragment
human monoclonal antibody: CT, clinical trial
human monoclonal antibody: AD, drug administration
human monoclonal antibody: DT, drug therapy
human monoclonal antibody: PK, pharmacokinetics
human monoclonal antibody: VI, intravitreal drug administration
nonsteroid antiinflammatory agent: PD, pharmacology
cyclooxygenase 1 inhibitor: AD, drug administration
cyclooxygenase 1 inhibitor: PK, pharmacokinetics
cyclooxygenase 1 inhibitor: PD, pharmacology
cyclooxygenase 1 inhibitor: TP, topical drug administration
cyclooxygenase 2 inhibitor: AD, drug administration
cyclooxygenase 2 inhibitor: PK, pharmacokinetics
cyclooxygenase 2 inhibitor: PD, pharmacology
cyclooxygenase 2 inhibitor: TP, topical drug administration
nitric oxide synthase: AD, drug administration
nitric oxide synthase: DT, drug therapy
nitric oxide synthase: PD, pharmacology
nitric oxide synthase: PO, oral drug administration
n(g) methylarginine: AD, drug administration
n(g) methylarginine: DT, drug therapy
n(g) methylarginine: PD, pharmacology
n(g) methylarginine: PO, oral drug administration
monoclonal antibody 1m 609: CT, clinical trial
monoclonal antibody 1m 609: DT, drug therapy
monoclonal antibody 1m 609: PD, pharmacology
proteinase inhibitor: DT, drug therapy
proteinase inhibitor: PD, pharmacology
plasminogen activator inhibitor 1: EC, endogenous compound
tissue inhibitor of metalloproteinase 1: EC, endogenous compound
angiostatin: EC, endogenous compound
angiogenesis inhibitor: EC, endogenous compound
unindexed drug
unclassified drug

CAS REGISTRY NO.: (vasculotropin) 127464-60-2; (pigment epithelium derived factor) 197980-93-1; (combretastatin A4) **117048-59-6**; (vasculotropin receptor) 301253-48-5; (rhodopsin) 60383-01-9, 9009-81-8; (growth hormone) 36992-73-1, 37267-05-3, 66419-50-9, 9002-72-6; (somatomedin C) 67763-96-6; (angiopoietin 1) 186270-49-5; (angiopoietin 2) 194368-66-6; (iodine 125) 14158-31-7, 22822-81-7; (nitric oxide synthase) 125978-95-2; (n(g) methylarginine) 156706-47-7, **17035-90-4**; (proteinase inhibitor) 37205-61-1; (plasminogen activator inhibitor 1) 140208-23-7; (tissue inhibitor of metalloproteinase 1) 140208-24-8; (angiostatin) 172642-30-7, 86090-08-6

CHEMICAL NAME: Vitaxin

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ACCESSION NUMBER: 2002111730 EMBASE
TITLE: Protease-mediated fragmentation of p-amidobenzyl ethers: A new strategy for the activation of anticancer prodrugs.
AUTHOR: Toki B.E.; Cerveny C.G.; Wahl A.F.; Senter P.D.
CORPORATE SOURCE: P.D. Senter, Seattle Genetics, 21823 30th Drive SE,

Bothell, WA 98021, United States. psenter@seagen.com
SOURCE: Journal of Organic Chemistry, (22 Mar 2002) 67/6 (1866-1872).
Refs: 42
ISSN: 0022-3263 CODEN: JOCEAH
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 016 Cancer
030 Pharmacology
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English
ABSTRACT:
A new anticancer prodrug activation strategy based on the 1,6-elimination reaction of p-aminobenzyl ethers is described. Model studies were undertaken with the N-protected peptide benzyloxycarbonylvaline-citrulline (Z-val-cit), which was attached to the amino groups of p-aminobenzyl ether derivatives of 1-naphthol and N-acetylnorephedrine. The amide bond that formed was designed for hydrolysis by cathepsin B, a protease associated with rapidly growing and metastatic carcinomas. Upon treatment with the enzyme, the Z-val-cit-p-amidobenzyl ether of 1-naphthol (2) underwent peptide bond hydrolysis with the rapid release of 1-naphthol. The aliphatic Z-val-cit-p-amidobenzyl ether of N-acetylnorephedrine (5) also underwent amide bond hydrolysis, but without the ensuing elimination of N-acetylnorephedrine. On the basis of these results, the phenolic anticancer drugs etoposide (6) and combretastatin A-4 (7) were attached to the Z-val-cit-p-amidobenzyl alcohol through ether linkages, forming the peptide-drug derivatives 8 and 9, respectively. Both compounds were stable in aqueous buffers and serum and underwent ether fragmentation upon treatment with cathepsin B, resulting in the release of the parent drugs in chemically unmodified forms. The released drugs were 13-50 times more potent than were the prodrug precursors on a panel of cancer cell lines. In contrast, the corresponding carbonate derivative of combretastatin A-4 (13) was unstable in aqueous environments and was as cytotoxic as combretastatin A-4. This result extends the use of the self-immolative p-aminobenzyl group for the fragmentation of aromatic ethers and provides a new strategy for anticancer prodrug development.

CONTROLLED TERM: Medical Descriptors:
reaction analysis
molecular model
chemical bond
hydrolysis
aqueous solution
human
controlled study
human cell
article
Drug Descriptors:
*proteinase
*antineoplastic agent: AN, drug analysis
*antineoplastic agent: CM, drug comparison
*prodrug: AN, drug analysis
*prodrug: CM, drug comparison
*benzyloxycarbonylvaline citrulline 4 amidobenzyl 3' o combretastatin A4: AN, drug analysis
*benzyloxycarbonylvaline citrulline 4 amidobenzyl 3' o combretastatin A4: CM, drug comparison
*citrulline: AN, drug analysis
*citrulline: CM, drug comparison
*peptide: AN, drug analysis
*peptide: CM, drug comparison
1 naphthol

norephedrine: AN, drug analysis
norephedrine: CM, drug comparison
n acetylnorephedrine: AN, drug analysis
n acetylnorephedrine: CM, drug comparison
etoposide: AN, drug analysis
etoposide: CM, drug comparison
combretastatin A4: AN, drug analysis
combretastatin A4: CM, drug comparison
cytotoxic agent: AN, drug analysis
cytotoxic agent: CM, drug comparison
cathepsin B
unclassified drug

CAS REGISTRY NO.: (proteinase) 9001-92-7; (citrulline) **372-75-8**; (1 naphthol) 90-15-3; (norephedrine) 700-65-2; (etoposide) 33419-42-0; (combretastatin A4) **117048-59-6**; (cathepsin B) 9047-22-7

L89 ANSWER 16 OF 27 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED. on STN

ACCESSION NUMBER: 2004149963 EMBASE
TITLE: Combretastatin A4 phosphate.
AUTHOR: West C.M.L.; Price P.
CORPORATE SOURCE: P. Price, Acad. Dept. of Radiation Oncology, Christie NHS Trust Hospital, Wilmslow Road, Manchester M20 4BX, United Kingdom. pat.price@man.ac.uk
SOURCE: Anti-Cancer Drugs, (2004) 15/3 (179-187).
Refs: 83
ISSN: 0959-4973 CODEN: ANTDEV
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 014 Radiology
016 Cancer
030 Pharmacology
037 Drug Literature Index
038 Adverse Reactions Titles
LANGUAGE: English
SUMMARY LANGUAGE: English
ABSTRACT:

Combretastatin A4 phosphate (CA4P) is a water-soluble prodrug of combretastatin A4 (CA4). The vascular targeting agent CA4 is a microtubule depolymerizing agent. The mechanism of action of the drug is thought to involve the binding of CA4 to tubulin leading to cytoskeletal and then morphological changes in endothellal cells. These changes increase vascular permeability and disrupt tumor blood flow. In experimental tumors, anti-vascular effects are seen within minutes of drug administration and rapidly lead to extensive ischemic necrosis in areas that are often resistant to conventional anti-cancer treatments. Following single-dose administration a viable tumor rim typically remains from which tumor regrowth occurs. When given in combination with therapies targeted at the proliferating viable rim, enhanced tumor responses are seen and in some cases cures. Results from the first clinical trials have shown that CA4P monotherapy is safe and reduces tumor blood flow. There has been some promising demonstration of efficacy. CA4P in combination with cisplatin is also safe. Functional imaging studies have been used to aid the selection of doses for phase II trials. Both dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI) and positron emission tomography can measure the anti-vascular effects of CA4P in humans. This review describes the background to the development of CA4P, its proposed mechanism of action, the results from the first clinical trials with CA4P and the role of imaging techniques in its clinical development. .COPYRGT. 2004 Lippincott Williams & Wilkins.

CONTROLLED TERM: Medical Descriptors:
drug mechanism

tumor blood flow
drug safety
drug efficacy
nuclear magnetic resonance imaging
positron emission tomography
endothelium cell
blood vessel permeability
tumor vascularization
cell growth
polymerization
protein phosphorylation
actin polymerization
antineoplastic activity
hyperthermia
radioimmunotherapy
fatigue: SI, side effect
lung toxicity: SI, side effect
hot flush: SI, side effect
pruritus: SI, side effect
nausea: SI, side effect
vomiting: SI, side effect
headache: SI, side effect
abdominal cramp: SI, side effect
QT prolongation: DI, diagnosis
QT prolongation: SI, side effect
cardiotoxicity: SI, side effect
blood toxicity: SI, side effect
syncope: SI, side effect
motor neuropathy: SI, side effect
ataxia: SI, side effect
thyroid cancer: DI, diagnosis
thyroid cancer: DT, drug therapy
kidney cancer: DT, drug therapy
lung non small cell cancer: DT, drug therapy
intestine ischemia: SI, side effect
maximum tolerated dose
area under the curve
human
nonhuman
clinical trial
review
priority journal
Drug Descriptors:
*combretastatin A4 phosphate: AE, adverse drug reaction
*combretastatin A4 phosphate: CT, clinical trial
*combretastatin A4 phosphate: CB, drug combination
*combretastatin A4 phosphate: DO, drug dose
*combretastatin A4 phosphate: DT, drug therapy
*combretastatin A4 phosphate: PK, pharmacokinetics
*combretastatin A4 phosphate: PD, pharmacology
*combretastatin A4 phosphate: IV, intravenous drug administration
combretastatin A4: CT, clinical trial
combretastatin A4: PR, pharmaceutics
combretastatin A4: PD, pharmacology
tubulin: EC, endogenous compound
cisplatin: CB, drug combination
colchicine: EC, endogenous compound
mitoflaxone
tumor necrosis factor alpha
vincristine
vinblastine

antibody
toxin
5,6 dimethylxanthenone 4 acetic acid
Vinca alkaloid
actin: EC, endogenous compound
myosin: EC, endogenous compound
growth factor
cytokine
myosin light chain: EC, endogenous compound
Rho kinase: EC, endogenous compound
Rho guanosine triphosphatase
nitric oxide synthase: EC, endogenous compound
carboplatin: CB, drug combination
doxorubicin: CB, drug combination
cyclophosphamide: CB, drug combination
fumagillol chloroacetylcarbamate: CB, drug combination
fluorouracil: CB, drug combination
iodine 125
carcinoembryonic antibody: CB, drug combination
gadolinium pentetate: IV, intravenous drug administration
nitric oxide synthase inhibitor

CAS REGISTRY NO.: (combretastatin A4 phosphate) **168555-66-6**, **222030-63-9**; (combretastatin A4) **117048-59-6**; (cisplatin) 15663-27-1, 26035-31-4, 96081-74-2; (colchicine) 64-86-8; (mitoflaxone) 87626-55-9; (vincristine) 57-22-7; (vinblastine) 865-21-4; (nitric oxide synthase) 125978-95-2; (carboplatin) 41575-94-4; (doxorubicin) 23214-92-8, 25316-40-9; (cyclophosphamide) 50-18-0; (fumagillol chloroacetylcarbamate) 129298-91-5; (fluorouracil) 51-21-8; (iodine 125) 14158-31-7, 22822-81-7; (gadolinium pentetate) 80529-93-7

CHEMICAL NAME: Tnp 470

L89 ANSWER 17 OF 27 EMBASE
on STN

ACCESSION NUMBER: 2002216312 EMBASE
TITLE: Small-molecule, tubulin-binding compounds as vascular targeting agents.
AUTHOR: Marx M.A.
CORPORATE SOURCE: Dr. M.A. Marx, Pfizer Global Research/Development, Pfizer Corporation, Eastern Point Road, Groton, CT 06340, United States
SOURCE: Expert Opinion on Therapeutic Patents, (2002) 12/6 (769-776).
Refs: 38
ISSN: 1354-3776 CODEN: EOTPEG
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 016 Cancer
030 Pharmacology
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English
ABSTRACT:
Vascular targeting or vascular damaging agents are directed toward established blood vessels, making them different from antiangiogenic agents, which inhibit one or more of the processes of neo-vascularisation. This emerging area of cancer drug discovery is currently being clinically tested and there is growing activity directed toward the identification of new antivascular agents. This review summarises key aspects of recent patents and patent applications referring to cancer chemotherapy and cancer drug discovery that involve the targeting or destruction of established vasculature. This review focuses on

applications that have been published between January 2000 and December 2001, with earlier, selected references included. Small molecule approaches, such as analogues of combretastatin A-4 (CA4) and colchicine, as well as other novel chemotypes, are the major focus of this review.

CONTROLLED TERM: Medical Descriptors:
protein binding
drug targeting
blood vessel
blood vessel injury
cancer chemotherapy
drug identification
patent
tumor vascularization
neovascularization (pathology)
drug mechanism
antineoplastic activity
drug structure
structure activity relation
dose response
nonhuman
mouse
controlled study
review
Drug Descriptors:
***combretastatin A4: AN, drug analysis**
***combretastatin A4: DV, drug development**
***combretastatin A4: PD, pharmacology**
*colchicine: AN, drug analysis
*colchicine: DV, drug development
*colchicine: PD, pharmacology
tubulin: EC, endogenous compound
angiogenesis inhibitor
prodrug: AN, drug analysis
prodrug: PD, pharmacology
combretastatin A4 phosphate: AN, drug analysis
combretastatin A4 phosphate: PD, pharmacology
stilbene: AN, drug analysis
stilbene: PD, pharmacology
stilbene derivative: AN, drug analysis
stilbene derivative: PD, pharmacology
combretastatin
combretastatin A1: AN, drug analysis
combretastatin A1: DV, drug development
combretastatin A1: PD, pharmacology
combretastatin B1: AN, drug analysis
combretastatin B1: DV, drug development
combretastatin B1: PD, pharmacology
combretastatin derivative: CB, drug combination
combretastatin derivative: PD, pharmacology
nitric oxide synthase inhibitor: CB, drug combination
nitric oxide synthase inhibitor: PD, pharmacology
aminoguanidine: PD, pharmacology
carboxylic acid
phosphate
sulfate
carbonic acid
cisplatin: CB, drug combination
cisplatin: PD, pharmacology
hydroxyphenstatin: AN, drug analysis
hydroxyphenstatin: DV, drug development

hydroxyphenstatin: PD, pharmacology
dioxostatin: AN, drug analysis
dioxostatin: DV, drug development
dioxostatin: PD, pharmacology
colchicine derivative: AN, drug analysis
colchicine derivative: DV, drug development
colchicine derivative: PD, pharmacology
n acetylcolchinol: AN, drug analysis
n acetylcolchinol: CM, drug comparison
n acetylcolchinol: DV, drug development
n acetylcolchinol: PD, pharmacology
zd 6126: AN, drug analysis
zd 6126: CB, drug combination
zd 6126: DV, drug development
zd 6126: DO, drug dose
zd 6126: PD, pharmacology
paclitaxel: CB, drug combination
nocodazole: AN, drug analysis
nocodazole: PD, pharmacology
nocodazole derivative: AN, drug analysis
nocodazole derivative: DV, drug development
nocodazole derivative: PD, pharmacology
benzothiophene: PD, pharmacology
polycyclic aromatic hydrocarbon derivative: PD, pharmacology
unindexed drug
unclassified drug

CAS REGISTRY NO.: (combretastatin A4) **117048-59-6**; (colchicine) 64-86-8; (stilbene) 588-59-0; (combretastatin) 82855-09-2, 89064-44-8; (aminoguanidine) 1068-42-4, 2582-30-1, **79-17-4**; (phosphate) 14066-19-4, 14265-44-2; (sulfate) 14808-79-8; (carbonic acid) 3812-32-6, 463-79-6; (cisplatin) 15663-27-1, 26035-31-4, 96081-74-2; (paclitaxel) 33069-62-4; (nocodazole) 31430-18-9; (benzothiophene) 95-15-8
CHEMICAL NAME: (1) Zd 6126; (2) Zd 6126
COMPANY NAME: (1) Astra Zeneca; (2) Angiogene; Oxigene

L89 ANSWER 18 OF 27 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED. on STN
ACCESSION NUMBER: 2002182701 EMBASE
TITLE: Angiogenesis: From the molecular mechanisms to the development of new drugs.
AUTHOR: Morbidelli L.; Donnini S.; D'Amore V.; Ziche M.
CORPORATE SOURCE: L. Morbidelli, Istituto di Scienze Farmacologiche, Universita di Siena, Siena, Italy
SOURCE: Acta Medica Romana, (2001) 39/2 (238-246).
Refs: 24
ISSN: 0001-6098 CODEN: AMROBA
COUNTRY: Italy
DOCUMENT TYPE: Journal; Conference Article
FILE SEGMENT: 005 General Pathology and Pathological Anatomy
030 Pharmacology
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English; Italian
ABSTRACT:
The steps required for new vessel growth are biologically complex and require coordinate regulation of contributing components, including modifications of cell-cell interactions, proliferation and migration of endothelial cells and matrix degradation. The observation that in vivo angiogenesis is accompanied by vasodilation, that many angiogenesis effectors possess vasodilating properties

and that tumor vasculature is in a persistent state of vasodilation, support the existence of a molecular/biochemical link between vasodilation and angiogenesis. Several pieces of evidence converge in the indication of a role for nitric oxide (NO), the factor responsible for vasodilation, in physiological and pathological angiogenesis. Data originated in different labs indicate that NO can act both as an "actor" of angiogenesis and as a "director of angiogenesis", both functions being equally expressed during physiological and pathological processes. NO significantly contributes to the prosurvival/proangiogenic program of capillary endothelium by triggering and transducing cell growth and differentiation via endothelial-constitutive NO synthase (ec-NOS) activation, cyclic GMP (cGMP) elevation, mitogen activated kinase (MAPK) activation and fibroblast growth factor-2 (FGF-2) expression. Re-establishment of a balanced NO production in the cardiovascular system results in a reduction of cell damage during inflammatory and vascular diseases. Elevation of NOS activity in correlation with angiogenesis and tumor progression has been extensively reported in experimental and human tumors. Tumor expansion and edema formation are sensitive to NOS inhibition. On this basis, the nitric oxide pathway appears to be a promising target for consideration in pro- and antiangiogenic therapeutic strategies. The use of NOS inhibitors seems appropriate to reduce edema, block angiogenesis and facilitate antitumor drug delivery.

CONTROLLED TERM: Medical Descriptors:
*angiogenesis
*neovascularization (pathology): ET, etiology
drug screening
regulatory mechanism
cell interaction
cell proliferation
cell migration
endothelium cell
extracellular matrix
in vivo study
vasodilatation
tumor vascularization
pathogenesis
capillary endothelium
signal transduction
cell growth
cell differentiation
enzyme activation
cell level
protein expression
mediator release
inflammation
vascular disease
enzyme activity
correlation analysis
tumor growth
edema: ET, etiology
enzyme inhibition
drug targeting
drug mechanism
drug delivery system
human
nonhuman
conference paper
Drug Descriptors:
*angiogenesis inhibitor: PD, pharmacology
nitric oxide: EC, endogenous compound
nitric oxide synthase: EC, endogenous compound
cyclic GMP: EC, endogenous compound

mitogen activated protein kinase: EC, endogenous compound
fibroblast growth factor 2: EC, endogenous compound
batimastat: PD, pharmacology
marimastat: PD, pharmacology
prinomastat: PD, pharmacology
ae 941: PD, pharmacology
amiloride: PD, pharmacology
minocycline: PD, pharmacology
monoclonal antibody lm 609: PD, pharmacology
benzodiazepine derivative: PD, pharmacology
endostatin: PD, pharmacology
alpha interferon: PD, pharmacology
gamma interferon: PD, pharmacology
interleukin 12: PD, pharmacology
nitric oxide synthase inhibitor: PD, pharmacology
thrombospondin 1: PD, pharmacology
fumagillol chloroacetylcarbamate: PD, pharmacology
combretastatin A4: PD, pharmacology
thalidomide: PD, pharmacology
roquinimex: PD, pharmacology
thrombocyte factor 4: PD, pharmacology
suramin: PD, pharmacology
distamycin A: PD, pharmacology
protamine: PD, pharmacology
acetylsalicylic acid: PD, pharmacology
unindexed drug

AS REGISTRY NO.: (nitric oxide) 10102-43-9; (nitric oxide synthase) 125978-95-2; (cyclic GMP) 7665-99-8; (mitogen activated protein kinase) 142243-02-5; (batimastat) 130370-60-4, 130464-84-5; (marimastat) 154039-60-8; (prinomastat) 192329-42-3, 195008-93-6; (amiloride) 2016-88-8, 2609-46-3; (minocycline) 10118-90-8, 11006-27-2, 13614-98-7; (endostatin) 187888-07-9; (gamma interferon) 82115-62-6; (interleukin 12) 138415-13-1; (thrombospondin 1) 343987-56-4; (fumagillol chloroacetylcarbamate) 129298-91-5; (combretastatin A4) **117048-59-6**; (thalidomide) 50-35-1; (roquinimex) 84088-42-6; (thrombocyte factor 4) 37270-94-3, 69670-74-2; (suramin) 129-46-4, 145-63-1; (distamycin A) 13696-04-3, 39389-47-4, 636-47-5; (protamine) 11061-43-1, 9007-31-2, 9012-00-4; (acetylsalicylic acid) 493-53-8, 50-78-2, 53663-74-4, 53664-49-6, 63781-77-1

HEMICAL NAME: Ag 3340; Lm 609; Vitaxin; Tnp 470; Aspirin

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CCESSION NUMBER: 1998235577 EMBASE

ITLE: Modification of tumor blood flow: Current status and future directions.

UTHOR: Chaplin D.J.; Hill S.A.; Bell K.M.; Tozer G.M.

ORPORATE SOURCE: D.J. Chaplin, Tumour Microcirculation Group, Gray Lab. Cancer Research Trust, Mount Vernon Hospital, Northwood, Middlesex HA6 2JR, United Kingdom

OURCE: Seminars in Radiation Oncology, (1998) 8/3 (151-163).
Refs: 122
ISSN: 1053-4296 CODEN: SRONEO

OUNTRY: United States

OCUMENT TYPE: Journal; General Review

ILE SEGMENT: 005 General Pathology and Pathological Anatomy
016 Cancer
030 Pharmacology
037 Drug Literature Index

ANGUAGE: English
JMMARY LANGUAGE: English
3STRACT:
ıboptimal drug distribution and hypoxia, which can contribute to treatment ailure, are e direct consequence of the spatial and temporal heterogeneity in erfusion that occurs in solid tumors. Therefore, improvements in tumor blood low have wide-ranging therapeutic importance. Paradoxically, controlled ecreases in tumor blood flow can also be exploited and, if permanent, induce xtensive tumor cell death on their own. We review the current knowledge of the actors controlling tumor blood flow with emphasis on the roles of the ndogeneous vasodilator nitric oxide and the endogenous vasoconstrictor ndothelin-1. The potential importance and application of approaches that rreversibly damage vascular function, so- called vascular targeting, are also ıscussed. Emphasis is given to the drug- based approaches to vascular argeting that are now entering clinical evaluation. There is no doubt that ncreased understanding of the processes that determine blood flow in tumors, oupled with the availability of techniques to monitor blood flow noninvasively ı the clinic, will enable strategies for selectively modifying tumor blood low to be transferred from the laboratory to the clinical setting.

ONTROLLED TERM: Medical Descriptors:
*tumor blood flow
*tumor vascularization
*antineoplastic activity
drug distribution
hypoxia: ET, etiology
treatment failure
angiogenesis
metastasis potential: CO, complication
drug delivery system
perfusion pressure
vascular resistance
vasoconstriction
vasodilatation
hyperthermic therapy
human
nonhuman
review
priority journal
Drug Descriptors:
***nitric oxide: EC, endogenous compound**
*endothelin 1: EC, endogenous compound
*antineoplastic agent: PK, pharmacokinetics
*antineoplastic agent: PD, pharmacology
*nitric oxide synthase: EC, endogenous compound
*angiogenesis inhibitor: PD, pharmacology
n(g) nitroarginine methyl ester
n(g) methylarginine
n(g) nitroarginine
diethylamine
endothelin receptor: EC, endogenous compound
oxygen
carbon dioxide
angiotensin: PD, pharmacology
hydralazine: DO, drug dose
hydralazine: PD, pharmacology
nicotinamide: PD, pharmacology
mitoflaxone: PD, pharmacology
dimethylxanthenone acetic acid: PD, pharmacology
colchicine: PD, pharmacology
combretastatin a4: DV, drug development
combretastatin a4: PD, pharmacology

tumor necrosis factor alpha: PD, pharmacology
unclassified drug

CAS REGISTRY NO.: (nitric oxide) 10102-43-9; (nitric oxide synthase) 125978-95-2; (n(g) nitroarginine methyl ester) 50903-99-6; (n(g) methylarginine) **17035-90-4**; (n(g) nitroarginine) **2149-70-4**; (diethylamine) 109-89-7, 660-68-4; (oxygen) 7782-44-7; (carbon dioxide) 124-38-9, 58561-67-4; (angiotensin) 11128-99-7, 1407-47-2; (hydralazine) 304-20-1, 86-54-4; (nicotinamide) 11032-50-1, 98-92-0; (mitoflaxone) 87626-55-9; (colchicine) 64-86-8; (combretastatin a4) **117048-59-6**

L89 ANSWER 20 OF 27 BIOTECHNO COPYRIGHT 2004 Elsevier Science B.V. on STN
DUPLICATE

ACCESSION NUMBER: 2002:35386461 BIOTECHNO

TITLE: Gephyrin **interacts** with dynein light chains 1 and 2, components of motor protein complexes

AUTHOR: Fuhrmann J.C.; Kins S.; Rostaing P.; El Far O.; Kirsch J.; Sheng M.; Triller A.; Betz H.; Kneussel M.

CORPORATE SOURCE: H. Betz, Max-Planck-Inst. for Brain Research, Department of Neurochemistry, Deutschordenstrasse 46, D-60528 Frankfurt/Main, Germany.
E-mail: neurochemie@mpih-frankfurt.mpg.de

SOURCE: Journal of Neuroscience, (01 JUL 2002), 22/13 (5393-5402), 53 reference(s)
CODEN: JNRSDS ISSN: 0270-6474

DOCUMENT TYPE: Journal; Article

COUNTRY: United States

LANGUAGE: English

SUMMARY LANGUAGE: English

ABSTRACT: The clustering of glycine receptors and major subtypes of GABA.sub.A receptors at inhibitory synapses is mediated by the **tubulin-binding** protein gephyrin. In an attempt to identify additional components of inhibitory postsynaptic specializations, we performed a yeast two-hybrid screen using gephyrin as bait. Multiple positive clones encoded either the dynein light chain-1 (Dlc-1), also known as dynein LC8 and protein **inhibitor** of neuronal **nitric oxide** synthase, or its homolog Dlc-2. Dlc-1 protein bound efficiently to gephyrin in in vitro binding assays and colocalized with gephyrin during coexpression in HEK293 cells. The binding site for Dlc was mapped to a fragment of 63 amino acids within the central linker domain of gephyrin. In hippocampal neurons, endogenous Dlc protein was enriched at synaptic sites identified by synaptophysin and gephyrin immunostaining. Immunoelectron microscopy in spinal cord sections revealed Dlc immunoreactivity at the edges of postsynaptic differentiations, in close contact with cytoskeletal structures and at the periphery of the Golgi apparatus. Because Dlc-1 and Dlc-2 have been described as stoichiometric components of cytoplasmic dynein and myosin-Va complexes, our results suggest that motor proteins are involved in the subcellular localization of gephyrin.

CONTROLLED TERM: *protein binding; *nucleotide sequence; *gephyrin; *dynein adenosine triphosphatase; *dynein light chain 1; *dynein light chain 2; complex formation; postsynaptic inhibition; two hybrid system; binding assay; protein protein **interaction**; protein

localization; protein expression; cell line; binding site; amino acid sequence; protein domain; hippocampus; immunohistochemistry; immunoelectron microscopy; spinal cord; cytoskeleton; immunoreactivity; Golgi complex; stoichiometry; human; human cell; article; priority journal; protein inhibitor; **nitric oxide** synthase **inhibitor**; synaptophysin; unclassified drug
CAS REGISTRY NUMBER: (gephyrin) 147570-97-6
GENE NUMBER: GENBANK AY034383 submitted number

L89 ANSWER 21 OF 27 BIOTECHNO COPYRIGHT 2004 Elsevier Science B.V. on STN
DUPLICATE
ACCESSION NUMBER: 1992:22077141 BIOTECHNO
TITLE: The 93 kDa protein gephyrin and tubulin associated with the inhibitory glycine receptor are phosphorylated by an endogenous protein kinase
AUTHOR: Langosch D.; Hoch W.; Betz H.
CORPORATE SOURCE: Abteilung Neurochemie, Max-Planck-Institut, fur Hirnforschung, Deutschordenstrasse 46,D-6000 Frankfurt 71, Germany.
SOURCE: FEBS Letters, (1992), 298/2-3 (113-117)
CODEN: FEBLAL ISSN: 0014-5793
DOCUMENT TYPE: Journal; Article
COUNTRY: Netherlands
LANGUAGE: English
SUMMARY LANGUAGE: English
ABSTRACT: The 93 kDa protein gephyrin is a **tubulin binding** peripheral membrane protein that is associated with the inhibitory glycine receptor and has been implicated in its anchoring at central synapses. Here, we demonstrate that gephyrin as well as co-purifying tubulin are phosphorylated by a kinase activity which is endogenous to highly purified glycine receptor preparations. This kinase phosphorylates serine and threonine residues and utilizes ATP, but not GTP, as phosphate donor. Its activity is not affected by various activators and/or inhibitors of cyclic nucleotide-dependent kinases, calcium/calmodulin-dependent kinases, or protein kinase C. A five-fold stimulation of kinase activity was, however, observed in the presence of poly-**lysine**. Phosphorylation of gephyrin and/or tubulin might regulate receptor/cytoskeleton **interactions** at postsynaptic membrane specializations.
CONTROLLED TERM: *glycine receptor; *membrane protein; *protein kinase; *tubulin; *protein phosphorylation; gephyrin; article; priority journal
CAS REGISTRY NUMBER: (protein kinase) 9026-43-1; (gephyrin) 147570-97-6

L89 ANSWER 22 OF 27 TOXCENTER COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2002:69138 TOXCENTER
COPYRIGHT: Copyright 2004 ACS
TITLE: Protease mediated fragmentation of p-amidobenzylethers: A new strategy for the activation of anticancer prodrugs
AUTHOR(S): Toki, Brian E.; Senter, Peter
CORPORATE SOURCE: Seattle Genetics, Bothell, WA, 98021, USA.
SOURCE: Abstracts of Papers, 223rd ACS National Meeting, Orlando, FL, United States, April 7-11, 2002, (2002) pp. MEDI-197.
CODEN: 69CKQP.
COUNTRY: UNITED STATES

DOCUMENT TYPE: Conference
FILE SEGMENT: CAPLUS
OTHER SOURCE: CAPLUS 2002:190316
LANGUAGE: English
ENTRY DATE: Entered STN: 20020319
Last Updated on STN: 20020319

ABSTRACT:
A new anticancer prodrug activation strategy based on the 1,6-elimination reaction of p-aminobenzyl ethers is described. Model studies were undertaken with the peptide Z-valine-**citrulline** (Z-val-cit), which was attached to the amino groups of p-aminobenzyl ether derivs. of 1-naphthol and N-acetylnorephedrine. The amide bond formed was designed for hydrolysis by cathepsin B, a protease assocd. with rapidly growing and metastatic carcinomas. Upon treatment with the enzyme, the Z-val-cit-p-amidobenzyl ether of 1-naphthol underwent peptide bond hydrolysis with rapid release of 1-naphthol. The aliph. Z-val-cit-p-amidobenzyl ether of N-acetylnorephedrine also underwent amide bond hydrolysis, but without the ensuing elimination of N-acetylnorephedrine. Based on these results, the phenolic anticancer **drugs**, etoposide and ***combretastatin*** **A-4** were attached to the Z-val-cit-p-amidobenzyl alc. through ether linkages. Both compds. were stable in aq. buffers and serum, and underwent ether fragmentation upon treatment with cathepsin B, resulting in the release of the parent drugs in chem. unmodified form. The released drugs were 13-22 times more potent that the prodrug precursors on a panel of cancer cell lines. In contrast, the corresponding carbonate deriv. of **combretastatin A-4** was unstable in aq. environments and was as cytotoxic as **combretastatin** ***A*** **-4**. This extends the use of the self-immolative p-aminobenzyl group for the fragmentation of arom. ethers and provides a new strategy for anticancer prodrug development.

L89 ANSWER 23 OF 27 TOXCENTER COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1997:34147 TOXCENTER
DOCUMENT NUMBER: PubMed ID: 9190213
TITLE: Functional **interactions** between the proline-rich and repeat regions of tau enhance microtubule binding and assembly
AUTHOR(S): Goode B L; Denis P E; Panda D; Radeke M J; Miller H P; Wilson L; Feinstein S C
CORPORATE SOURCE: Department of Molecular, Cellular, and Developmental Biology, University of California, Santa Barbara 93106, USA
CONTRACT NUMBER: NS13560 (NINDS)
NS35010 (NINDS)
SOURCE: Molecular biology of the cell, (1997 Feb) 8 (2) 353-65. Journal Code: 9201390. ISSN: 1059-1524.
COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
FILE SEGMENT: MEDLINE
OTHER SOURCE: MEDLINE 97206133
LANGUAGE: English
ENTRY DATE: Entered STN: 20011116
Last Updated on STN: 20011116

ABSTRACT:
Tau is a neuronal microtubule-associated protein that promotes microtubule assembly, stability, and bundling in axons. Two distinct regions of tau are important for the tau-microtubule **interaction**, a relatively well-characterized "repeat region" in the carboxyl terminus (containing either three or four imperfect 18-amino acid repeats separated by 13- or 14-amino acid long inter-repeats) and a more centrally located, relatively poorly characterized proline-rich region. By using amino-terminal truncation analyses of tau, we have localized the microtubule binding activity of the proline-rich region to Lys215-Asn246 and identified a small sequence within this region,

215KKVAVVR221, that exerts a strong influence on microtubule binding and assembly in both three- and four-repeat tau isoforms. Site-directed mutagenesis experiments indicate that these capabilities are derived largely from Lys215/Lys216 and Arg221. In marked contrast to synthetic peptides corresponding to the repeat region, peptides corresponding to Lys215-Asn246 and Lys215-Thr222 alone possess little or no ability to promote microtubule assembly, and the peptide Lys215-Thr222 does not effectively suppress in vitro microtubule dynamics. However, combining the proline-rich region sequences (Lys215-Asn246) with their adjacent repeat region sequences within a single peptide (Lys215-Lys272) enhances microtubule assembly by 10-fold, suggesting intramolecular **interactions** between the proline-rich and repeat regions. Structural complexity in this region of tau also is suggested by sequential amino-terminal deletions through the proline-rich and repeat regions, which reveal an unusual pattern of loss and gain of function. Thus, these data lead to a model in which efficient microtubule binding and assembly activities by tau require intramolecular **interactions** between its repeat and proline-rich regions. This model, invoking structural complexity for the microtubule-bound conformation of tau, is fundamentally different from previous models of tau structure and function, which viewed tau as a simple linear array of independently acting **tubulin-binding** sites.

CONTROLLED TERM: Check Tags: Support, Non-U.S. Gov't; Support, U.S. Gov't, Non-P.H.S.; Support, U.S. Gov't, P.H.S.
Amino Acid Sequence
Asparagine
Binding Sites
Lysine
*Microtubules: ME, metabolism
Microtubules: PH, physiology
Molecular Sequence Data
Peptides: CS, chemical synthesis
Peptides: CH, chemistry
Peptides: ME, metabolism
*Proline: ME, metabolism
Structure-Activity Relationship
tau Proteins: CH, chemistry
*tau Proteins: ME, metabolism

REGISTRY NUMBER: 147-85-3 (Proline)
56-87-1 (**Lysine**)
7006-34-0 (Asparagine)

CHEMICAL NAME: 0 (Peptides); 0 (proline-rich polypeptide); 0 (tau Proteins)

L89 ANSWER 24 OF 27 TOXCENTER COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1995:200494 TOXCENTER
COPYRIGHT: Copyright 2004 ACS
DOCUMENT NUMBER: CA12317225061D
TITLE: .tau. Protein from Alzheimer's disease patients is glycated at its **tubulin-binding** domain
AUTHOR(S): Ledesma, M. Dolores; Bonay, Pedro; Avila, Jesus
CORPORATE SOURCE: Centro Biologia Molecular "Severo Ochoa", Univ. Autonoma Madrid, Madrid, Spain.
SOURCE: Journal of Neurochemistry, (1995) Vol. 65, No. 4, pp. 1658-64.
CODEN: JONRA9. ISSN: 0022-3042.
COUNTRY: SPAIN
DOCUMENT TYPE: Journal
FILE SEGMENT: CAPLUS
OTHER SOURCE: CAPLUS 1995:817710
LANGUAGE: English
ENTRY DATE: Entered STN: 20011116
Last Updated on STN: 20030617

ABSTRACT:

Glycated residues of .tau. protein from paired helical filaments isolated from the brains of Alzheimer's disease patients were localized by doing a proteolytic cleavage of the protein, fractionation of the resulting peptides, and identification of those peptide using specific antibodies. The most suitable residues for glycation, lysines, present at the **tubulin-***binding*** motif of .tau. protein, seem to be preferentially modified compared with those lysines present at other regions. Among these modified lysines, those located in the sequence comprising residues 318-336 (in the largest human .tau. isoform) were found to be glycated, as detd. by the reaction with an antibody that recognizes a glycated peptide contg. this sequence. Because those lysines are present in a **tubulin** ***binding*** motif of .tau. protein, its modification could result in a decrease in the **interaction** of .tau. with tubulin.

CLASSIFICATION CODE: 14-10
SUPPLEMENTARY TERMS: Miscellaneous Descriptors
tau protein glycation tubulin domain Alzheimer
REGISTRY NUMBER: 56-87-1 (**Lysine**)

L89 ANSWER 25 OF 27 WPIDS COPYRIGHT 2004 THOMSON DERWENT on STN
ACCESSION NUMBER: 2003-239101 [23] WPIDS
DOC. NO. CPI: C2003-061206
TITLE: Novel compound useful for treating cancer, tumors and inflammatory diseases, cleavable by CD10, and has therapeutic agent capable of entering target cell, oligopeptide, stabilizing group and linker group.
DERWENT CLASS: A96 B04 D16
INVENTOR(S): BEBBINGTON, C R; CARDARELLI, P M; GANGWAR, S; NIEDER, M H; PAN, C; PICKFORD, L B
PATENT ASSIGNEE(S): (MEDA-N) MEDAREX INC; (BEBB-I) BEBBINGTON C R; (CARD-I) CARDARELLI P M; (GANG-I) GANGWAR S; (NIED-I) NIEDER M H; (PANC-I) PAN C; (PICK-I) PICKFORD L B
COUNTRY COUNT: 101
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG	MAIN IPC
WO 2002100353	A2	20021219	(200323)*	EN	167	A61K000-00
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ NL OA PT SD SE SL SZ TR TZ UG ZM ZW						
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ OM PH PL PT RO RU SD SE SG SI SK SL TJ TM TN TR TT TZ UA UG US UZ VN YU ZA ZM ZW						
EP 1404356	A2	20040407	(200425)	EN		A61K038-06
R: AL AT BE CH CY DE DK ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT RO SE SI TR						
US 2004087497	A1	20040506	(200430)			A61K038-17

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 2002100353	A2	WO 2002-US21135	20020610
EP 1404356	A2	EP 2002-746852	20020611
		WO 2002-US21135	20020611
US 2004087497	A1 Provisional	US 2001-297596P	20010611
		US 2002-167627	20020611

FILING DETAILS:

PATENT NO	KIND	PATENT NO

EP 1404356 A2 Based on WO 2002100353

PRIORITY APPLN. INFO: US 2001-297596P 20010611; US 2002-167627 20020611

INT. PATENT CLASSIF.:
MAIN: A61K000-00; A61K038-06; A61K038-17
SECONDARY: A61K031-337; A61K031-704; A61K031-7048; A61K031-7072; A61K031-7076; A61K038-07; A61K038-08; A61K038-13; C07K001-16; C07K005-08; C07K005-10; C07K007-06; C12Q001-37

BASIC ABSTRACT:

WO2002100353 A UPAB: 20030407

NOVELTY - A compound (I) comprising therapeutic agent (TA) capable of entering target cell, oligopeptide (OP), stabilizing group (SG) and optionally, linker group (LG), and cleavable by CD10, is new.

DETAILED DESCRIPTION - OP is directly linked to SG at first attachment site of OP and OP is directly linked to TA or indirectly linked through LG to TA at second attachment site of OP, and SG hinders cleavage of (I) by enzymes present in blood.

(I) comprises TA capable of entering a target cell, OP of the formula (AA)n-AA(P2)-AA(P1)-AA(P1')-(AA)m, where n and m are integers, AA(P2), AA(P1) and AA(P1') represents any amino acid, and each AA independently represents an amino acid, SG, and optionally, LG, where (I) is cleavable by CD10, OP is directly linked to SG at a first attachment site of OP and OP is directly linked to TA or indirectly linked through LG to TA at a second attachment site of OP, SG hinders cleavage of (I) by enzymes present in whole blood, if OP is Leu-Ala-Leu, then SG is not succinyl or beta Ala or TA is not one of doxorubicin and daunorubicin, if OP is beta Ala-Leu-Ala-Leu, then SG is not succinyl or TA is not one of doxorubicin and daunorubicin, if OP is beta Ala-Leu-Ala-Leu, then SG is not glutaryl or TA is not doxorubicin, and (I) is not chosen from Succ-Ala-Leu-Ala-Leu-Dnr, pGlu-Ala-Leu-Ala-Leu-Dox, D-Ala-Leu-Ala-Leu-Dnr, D-Leu-Ala-Leu-Ala-Leu-Dnr, D-Leu-D-Ala-Leu-Ala-Leu-Dnr, Acetyl-His-Ser-Ser-Lys-Leu-Gln-Dox, Morpholinocarbonyl-His-Ser-Ser-Lys-Leu-Gln-Leu-Dox, N-(2-hydroxypropyl)methacrylamide-Gly-Phe-Leu-Gly-Dox, N-glutaryl-(4-hydroxyprolyl)-Ala-Ser-Cyclohexylglycine- Gln-Ser-Leu-Dox, N-Cbz-Gly-Phe-Ala-Leu-Dox and N-Cbz-Gly-Phe-Ala-Leu-PABC-Dox.

INDEPENDENT CLAIMS are also included for:

(1) a conjugate (II) comprising OP which is cleavable by CD10 or thermolysin-like enzyme;

(2) a pharmaceutical composition (III) comprising (I) and a carrier;

(3) production (M) of (I);

(4) a prodrug produced by (M);

(5) screening to identify OP useful for designing a prodrug, by providing (I), and testing if OP is cleavable by CD10, where cleavability by CD10 is indicative of OP as a candidate for designing a prodrug; and

(6) an article of manufacture for diagnosis or assay comprising (I) which has a marker, OP, SG, and optionally LG not cleavable by CD10, and a reagent useful in the detection of the marker.

ACTIVITY - Cytostatic; Antiinflammatory; Anti-tumor.

The effect of Suc- beta Ala-Ile-Ala-Leu-Dox therapeutic agent on the survival of mice and on growth of the tumors in a mouse xenograft model was evaluated. Groups of ten nude mice, were subcutaneously implanted with chunks of doxorubicin-resistant colorectal carcinoma LS174t, and were allowed to grow to approximately 50 mg. They were treated intravenously with 0, 53 or 68 mg/kg of Suc- beta Ala-Ile-Ala-Leu-Dox (equivalent to 0, 30 or 38 mg/kg doxorubicin) at five day intervals for a total of five identical doses. Tumors and body weights were measured twice weekly for up to 60 days. Both doses were efficacious in reducing the growth of tumors compared with vehicle control animals. There were 4 and 2 long-term survivors in the low and high dose groups, respectively, compared with 0

in the vehicle control group. The Mean Day of Survival (MDS) in animals whose tumors reached 1.5 g prior to day 60 was significantly better in the low (29.7 days) and high (23.4 day) dose groups than in the vehicle control group (18.2 days). Thus, Suc- beta Ala-Ile-Ala-Leu-Dox was efficacious in this aggressive human tumor model, in which doxorubicin alone at its tolerated dose (3 mg/kg), under this dosing regimen, was ineffective.

MECHANISM OF ACTION - Inhibitor of tumor growth.

USE - (I) is useful for manufacturing a medicament for treating a disorder having CD10-associated target cells, such as cancer (e.g. prostate cancer, B-cell lymphoblastic leukemia, T-cell lymphoblastic leukemia, lymphoma, including B-cell lymphoma and non-Hodgkins' lymphoma, follicular lymphoma, Burkitt lymphoma, melanoma, ocular melanoma, cutaneous melanoma, colon adenocarcinomas, hepatocellular carcinomas, renal cell carcinoma, ovarian carcinoma, prostate adenocarcinoma, liver carcinoma, transitional cell carcinoma, pancreatic adenocarcinoma, lung carcinoma, breast carcinoma and colon carcinoma), neoplastic diseases, tumors, inflammatory diseases, and infectious diseases. The method involves detecting CD10 associated with a target cell, and administering (I) to the patient. The detecting step involves obtaining a sample of tissue, combining the sample with a CD10-specific antibody, and determining binding of the CD-10 specific antibody to the sample. (I) is also useful for decreasing toxicity of TA which is intended for administration to a patient, by covalently forming a prodrug by linking OP cleavable by CD10 to SG at a first attachment site of OP and directly or indirectly linking TA at a second attachment site of OP, so that the prodrug is cleavable by CD10. The prodrug allows for administration of an increased dosage of TA in prodrug form to the patient relative to the dosage of TA in unconjugated form (all claimed). (I) is useful for diagnosing CD10 positive tumors.

ADVANTAGE - (I) has high specificity of action, reduced toxicity, improved stability in the serum and blood, improved therapeutic index, favorable pharmacokinetics, and does not move into target cells, or moves only minimally until activated by CD10.

DESCRIPTION OF DRAWING(S) - The figure is a schematic diagram showing cleavage of a prodrug in the extracellular vicinity of the target cell and within the target cell.

Dwg.2/35

FILE SEGMENT: CPI
FIELD AVAILABILITY: AB; GI
MANUAL CODES: CPI: A12-V01; B04-B04D; B04-C01; B04-F01; B04-L01; B04-N04; B11-C07; B12-K04A; B12-K04E; B14-A01; B14-A02; B14-C03; B14-H01; D05-A02; D05-C11; D05-H09; D05-H17A6

L89 ANSWER 26 OF 27 SCISEARCH COPYRIGHT 2004 THOMSON ISI on STN
ACCESSION NUMBER: 1998:910300 SCISEARCH
THE GENUINE ARTICLE: 141VC
TITLE: Modification of tau to an Alzheimer's type protein interferes with its **interaction** with microtubules
AUTHOR: Gonzalez C; Farias G; Maccioni R B (Reprint)
CORPORATE SOURCE: UNIV CHILE, FAC SCI, MOL & CELLULAR BIOL LAB, CASILLA 70111, SANTIAGO 7, CHILE (Reprint); UNIV CHILE, FAC SCI, MOL & CELLULAR BIOL LAB, SANTIAGO 7, CHILE; INT CTR CANC & DEV BIOL, SANTIAGO 7, CHILE
COUNTRY OF AUTHOR: CHILE
SOURCE: CELLULAR AND MOLECULAR BIOLOGY, (NOV 1998) Vol. 44, No. 7, pp. 1117-1127.
Publisher: CELLULAR & MOLECULAR BIOLOGY, PROF R WEGMANN RESIDENCE HAUSSMANN 1 AVENUE DU PAVE NEUF, 93160 NOISY-LE-GRAND, FRANCE.

ISSN: 0145-5680.
DOCUMENT TYPE: Article; Journal
FILE SEGMENT: LIFE
LANGUAGE: English
REFERENCE COUNT: 45
ABSTRACT:

The microtubule associated protein tau is the main structural component of paired helical filaments (PHFs), aberrant polymers found intracellularly in neurons of brains with the Alzheimers disease. Glycation is one of the posttranslational modifications that has been found in tau from PHFs, but not in normal brain tau. Studies were carried out with purified tau protein subjected to chemical modifications, in order to further investigate the mechanisms of tau self-association into PHFs. Tau was subjected to modifications affecting reactive lysyl residues, e.g., carbamoylation with potassium cyanate and glycation reaction with glucose. The effects of these modifications to produce functional alterations in tau capacity to bind brain tubulin and to induce microtubule assembly were investigated. Chemically-modified tau and tau of Alzheimer's type exhibited a similar microtubule **interaction** behavior as analysed by overlay assays, but those were different than normal tau controls. On the other hand, studies of the microtubule assembly kinetics indicated that the reported tau modifications resulted in a loss of its capacity to promote microtubule assembly from purified tubulin preparations. The data on the differences in the electrophoretic profiles, Western blots and the overlay patterns, along with those on the microtubule polymerisation of normal brain tau as compared with both modified and Alzheimer's tau, suggest changes in the functional behavior of this protein as a result of its structural modifications. These studies were complemented with an immunogold analysis at the electron microscope level, which indicated that the modified tau did not incorporate into assembled microtubules. These findings, combined with the results on tau chemical modifications suggest that the reactive **lysine** residues within functional domains on tau, e.g., those of the repetitive binding motifs, were affected by these modifications. Furthermore, these observations provide new clues to understand the anomalous **interactions** of tau in Alzheimer's disease.

CATEGORY: CELL BIOLOGY; BIOCHEMISTRY & MOLECULAR BIOLOGY
SUPPLEMENTARY TERM: tau glycation; **tubulin binding**; microtubules; Alzheimer's disease
SUPPL. TERM PLUS: PAIRED HELICAL FILAMENTS; CHEMICALLY-MODIFIED-TAU; SYNTHETIC PEPTIDES; REGULATORY DOMAIN; IMMUNOLOGICAL CHARACTERIZATION; NEUROFIBRILLARY DEGENERATION; ABNORMAL PHOSPHORYLATION; DISEASE; TUBULIN; BINDING

REFERENCE(S):

Referenced Author (RAU)	Year (RPY)	VOL (RVL)	PG (RPG)	Referenced Work (RWK)
ALONSO A D	1997	94	298	P NATL ACAD SCI USA
BANCHER C	1989	477	90	BRAIN RES
BIERNAT J	1993	11	153	NEURON
BINDER L I	1985	101	1371	J CELL BIOL
BUSCIGLIO J	1995	14	879	NEURON
BUSCIGLIO J	1993	90	2092	P NATL ACAD SCI USA
CAMBIAZO V	1995	64	1288	J NEUROCHEM
CAPUTO C B	1992	13	267	NEUROBIOL AGING
CLEVELAND D W	1990	60	701	CELL
CROSS D	1996	229	378	EXP CELL RES
ENNULAT D J	1989	264	5327	J BIOL CHEM
FARIAS G	1997	168	59	MOL CELL BIOCHEM
FARIAS G A	1993	13	173	CELL MOL NEUROBIOL
FARIAS G A	1992	112	81	MOL CELL BIOCHEM
FLAMENT S	1990	516	15	BRAIN RES

GOEDERT M	1988	85	4051	P NATL ACAD SCI USA
GREENBERG S G	1990	87	5827	P NATL ACAD SCI USA
GRUNDKEIQBAL I	1986	83	4913	P NATL ACAD SCI USA
HERZOG W	1978	92	1	EUR J BIOCHEM
IMAHORI K	1997	121	179	J BIOCHEM-TOKYO
IQBAL K	1989	248	87	FEBS LETT
IQBAL K	1986	2	421	LANCET
LAEMMLI U K	1970	227	680	NATURE
LEDESMA M D	1994	269	21614	J BIOL CHEM
LEE G	1988	239	285	SCIENCE
LEE V M Y	1991	251	675	SCIENCE
LINDWALL G	1984	259	5301	J BIOL CHEM
LIU W K	1991	266	21723	J BIOL CHEM
LOWRY O H	1951	193	265	J BIOL CHEM
MACCIONI R B	1989	275	568	ARCH BIOCHEM BIOPHYS
MACCIONI R B	1995	20	34	CIENCIA HOJE
MACCIONI R B	1988	7	1957	EMBO J
MACCIONI R B	1986			MOL CYTOLOGY MICROTU
MACCIONI R B	1996	75	835	PHYSIOL REV
MACCIONI R B	1992		153	PROGR CELL BIOL
MELLADO W	1982	203	675	BIOCHEM J
NACHARAJU P	1997	69	1709	J NEUROCHEM
OLTERSDORF T	1990	265	4465	J BIOL CHEM
RIVAS C I	1988	85	6092	P NATL ACAD SCI USA
RIVASBERRIOS A	1990	1040	382	BIOCHIM BIOPHYS ACTA
SELDEN S C	1983	258	7064	J BIOL CHEM
STEINER B	1990	9	3539	EMBO J
VERA J C	1988	85	6763	P NATL ACAD SCI USA
WISCHIK C	1988	100	1905	J CELL BIOL
WISCHIK C M	1985	100	1905	J CELL BIOL

L89 ANSWER 27 OF 27 USPATFULL on STN
ACCESSION NUMBER: 2003:258371 USPATFULL
TITLE: Compositions with vascular damaging activity
INVENTOR(S): Davis, Peter David, Aston Rowant, UNITED KINGDOM

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2003181424	A1	20030925
APPLICATION INFO.:	US 2003-367606	A1	20030214 (10)

RELATED APPLN. INFO.: Continuation of Ser. No. WO 2001-GB3668, filed on 15 Aug 2001, UNKNOWN

	NUMBER	DATE
PRIORITY INFORMATION:	GB 2000-19944	20000815

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: LADAS & PARRY, 26 WEST 61ST STREET, NEW YORK, NY, 10023
NUMBER OF CLAIMS: 14
EXEMPLARY CLAIM: 1
LINE COUNT: 471
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB Compositions for the inhibition of the formation of new vaculature by angiogenesis are provided as in compounds which are salts comprising as an acidic component a compound of formula (1) wherein: R.sup.1, R.sup.2 and R.sup.3 are each independently alkyl, R.sup.4 is alkoxy, haloalkoxy, alkyl, haloalkyl, alkenyl, alkynyl, alkylthio, alkylsulphinyl, alkylsulphonyl, hydroxy or halo, R.sup.5 is hydrogen, alkoxy, alkyl,

alkylthio, hydroxy, phosphate or halo, and, as the basic component, a compound selected from the group consisting of (2) a compound of formula (2) wherein R.sup.6 is hydrogen or alkyl R.sup.7 is alkyl, alkylamino, dialkylamino, nitroamino, hydrazine, mercapto or alkylthio X is CH.sub.2, CH.sub.2CH.sub.2, CH.sub.2S, CH.sub.2CH.sub.2S Y is NH or S or a compound of formula (3) wherein R.sup.8 is alkyl or aminoalkyl R.sup.9 is hydrogen, alkyl or optionally substituted phenyl or, a compound of formula (4) wherein Z is 0, S, CH2, CHR13 or a bond R.sup.10, R.sup.11, R.sup.12 and R.sup.13 are each independently alkyl or hydrogen or, a compound of formula (5) wherein R.sup.14 is alkyl and the pharmaceutically acceptable solvates and hydrates thereof.

IT **222030-63-9**
(prepn. and use of cis-stilbene derivs. with vascular damaging activity)

IT **2149-70-4**
(prepn. and use of cis-stilbene derivs. with vascular damaging activity)

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